Review Article

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Recent advances of bioresponsive polymeric nanomedicine for cancer therapy

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ABSTRACT

A bioresponsive polymeric nanocarrier for drug delivery is able to alter its physical and physicochemical properties in response to a variety of biological signals and pathological changes, and can exert its therapeutic efficacy within a confined space. These nanosystems can optimize the biodistribution and subcellular location of therapeutics by exploiting the differences in biochemical properties between tumors and normal tissues. Moreover, bioresponsive polymer-based nanosystems could be rationally designed as precision therapeutic platforms by optimizing the combination of responsive elements and therapeutic components according to the patient-specific disease type and stage. In this review, recent advances in smart bioresponsive polymeric nanosystems for cancer chemotherapy and immunotherapy will be summarized. We mainly discuss three categories, including acidity-sensitive, redox-responsive, and enzyme-triggered polymeric nanosystems. The important issues regarding clinical translation such as reproducibility, manufacture, and probable toxicity, are also commented.

KEYWORDS

drug delivery, polymer, bioresponsive, immunotherapy, cancer therapy

1 Introduction

Tumor heterogeneity, unlimited proliferation capacity, and tumor metastasis pose great challenges to cancer treatment [1–5]. The therapeutic efficacy and safety profiles of current tumor treatments, such as immunotherapy and chemotherapy, are still unfavorable, which is largely ascribed to the poor biodistribution of therapeutic drugs [6, 7]. Further, these therapeutic drugs may induce unwanted side effects like uncontrolled immune-related systemic cytokine storm and cardiotoxicity [8]. With regard to the therapeutic efficacy, multiple drug resistance and limited immune responsiveness severely hinder their further applications [9–11]. Due to this, smart drug delivery systems (DDSs) offer distinct strategies to address these issues.

Among them, nanomedicine has achieved tremendous progress in cancer management [12–14]. Nanoparticles can protect the cargo from degradation and facilitate their accumulation at tumor sites through passive diffusion or active targeting, optimizing the drug biodistribution [15–19]. Especially in the past few years, nanocarriers that can respond to biological cues in the tumor microenvironment (TME) attracted increasing attention [20–22]. As one representative, responsive polymeric nanoparticles can achieve the precise release of drugs at the tumor site by exploiting the differences in physicochemical properties between tumor tissues and normal tissues, including pH, redox state, as well as particular enzymes (Fig. 1) [23–26]. The low pH, high concentration of reactive oxygen species (ROS) and glutathione (GSH), as well as overexpression of matrix metalloproteinase (MMP) in tumor tissues or cancer cells can act as responsive factors to achieve precise drug delivery [27, 28]. Along with mono-responsive polymers, dual- and multi-response polymeric nanomedicines have also been designed to counter more complicated intracellular and extracellular environmental cues, which enable more functional and controlled release of anticancer

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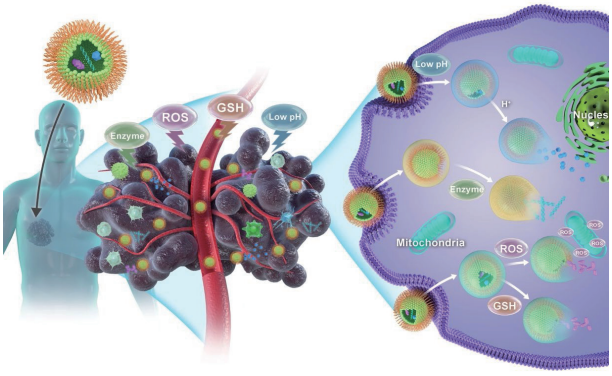

Figure 1 Schematic illustration of bioresponsive polymeric nanomedicines. pH-, redox state-, and enzyme-responsive polymeric nanosystems represent three major delivery platforms of bioresponsive polymeric nanomedicine.

therapeutical agents [29, 30]. Through rational design associated with physicochemical properties of carriers and their response capabilities towards various physicochemical signals in TME, bioresponsive polymeric nanoplatforms can act as the next-generation delivery vehicle to achieve improved therapeutic efficacy and biosafety for cancer treatments.

Herein, we first introduce the responsive mechanism of pH-, redox state-, and enzyme-responsive polymeric nanomedicine. Next, we will highlight the recent advances of these bioresponsive polymeric nanomedicines for cancer therapy. Meanwhile, the other bioresponsive materials for various diseases are also briefly introduced. Current roadblocks of bioresponsive polymers for cancer treatment are elucidated at the end of this review.

2 Bioresponsive polymeric nanomedicine

2.1 pH-responsive polymeric nanomedicine

The extracellular pH (pH_e) of healthy tissues and blood is maintained at 7.4, while their intracellular pH (pH_i) is 7.2 [31, 32]. Different from healthy tissues, tumor sites exhibit a lower pH_e than healthy tissues, and the pH gradient in most malignancies is inverted ($pH_i > pH_e$). pH_i in human patients shows a mean pH value of 7.0, varying from 5.7 to 7.8. This variance is determined by the volume, histology, and detection location of tumors [33]. Nanoparticles can partly accumulate in tumor sites via blood circulation by the enhanced permeability and retention (EPR) effect [34]. And depending on their physical and physiochemical properties, they can either release the drug directly in the TME or be taken up by the tumor cells. The pH responsiveness of the polymeric nanomedicines can be achieved via either the protonation of ionizable groups or the degradation of their acid–cleavable bonds [35]. Accordingly, a range of pH-responsive polymeric nanomedicines have been created for realizing spatiotemporally-controlled drug release, which can be generally classified into extracellular pH-responsive and cytosolic pH-responsive polymers.

2.1.1 Extracellular pH-responsive polymeric nanomedicine

The poor biodistribution and restricted tumor penetration of nanoparticles are two major obstacles for cancer therapies [36]. Research showed that the stealth nanoparticles typically apply the EPR mechanism to target tumors with the help of their high tendency to extravasate across tumor vasculatures and accumulate around blood vessels [37, 38]. However, the dense tumor matrix hinders the penetration and tumor accumulation of the large stealth nanoparticles [39, 40]. In opposed to that, nanoparticles can penetrate tumors deeply with the help of their low diffusional restriction, but they exhibit a shorter circulating half-life and less accumulation around tumor [41–43]. Accordingly, Li et al. developed pH-sensitive size-switchable sensitive cluster nanobombs (SCNs)/Pt nanoparticles to enhance tumor penetration [44]. In this study, SCNs/Pt was fabricated via self-assembly from poly (ethylene glycol)-(2-azepane ethyl methacrylate)-modified poly(amidoamine) (PAMAM) dendrimers (PEG-*b*-PAEMA-PAMAM/Pt) (Fig. 2(a)). At physiological pH, PAEMA was hydrophobic and promoted the assembly of PEG-*b*-PAEMA-PAMAM/Pt into SCNs/Pt. At the acidic TME, PAEMA swiftly protonated and became hydrophilic, resulting in the instant disintegration of SCNs/Pt into smaller particles for efficient tumor penetration (Figs. 2(b) and 2(c)). To verify this, BxPC-3 multicellular spheroids (MCSs) were used to test tumor penetration and tumor inhibition capability. As a consequence, even at a scanning depth of 85 μm, the red signals that represent nanoparticles within the MCSs were visible, which confirmed the bottomless penetration and consistent distribution capabilities of nanoparticles at acidic conditions. Additionally, SCNs/Pt achieved 82% tumor suppression with a 2 mg/kg dose in the mouse-bearing BxPC-3 xenograft tumor.

Adjusting the dimensions of nanoparticles to increase penetration depth into the tumor in responding to the pH variances is another strategy for improving delivery efficiency. The ability to regulate drug release precisely at the tumor site can inhibit drug leakage in normal tissues, thereby minimizing toxicity. However, when compared to the physiological pH (~ pH 7.4), the TME is slightly acidic (~ pH 7.0–6.5) [45]. Thus, more sensitive pH-responsive release systems are needed to meet this challenge.

Liu et al. recently developed a proton transistor nanodetergents (pTNTs) library. The pTNTs were capable of amplifying and transforming small pH disturbance into state transition in membranolytic activity, allowing selective plasma membrane rupture (PMR) for cancer treatment [46]. In this research, the pTNTs were built by a PEG block and a pH-responsive membranolytic block (MB). The MB contains ionizable tertiary amine segments (ethyl piperidine (C6)) and hydrophobic segments (C6-R_x). The mainstream of the tertiary amines was deprotonated and sheltered by a PEG shell, therefore retaining a low membranolytic state ("OFF" state). After a fast rise of C6 protonation in the low-pH environment, the pTNTs were converted into cationic nanoparticles, resulting in powerful membrane cleavage activity ("ON" state) (Fig. 2(d)). It should be noted that the library of P(C6-R_x) copolymers was screened for an optimized pTNT against Panc02 tumor cells (Fig. 2(e)). After 4 h of incubation, P(C6-Bn_{20}) displayed a more than 32-fold increase in cytotoxicity with a slight pH shift (0.1 pH). At pH 7.4, P(C6-Bn_{20}) exhibited a selective killing ability while causing minimal harm to cancer and normal cells. Following that, subsequent experiments showed that P(C6-Bn_{20}) exerted a cytotoxic outcome for tumor cells via a membranolytic manner under acidic conditions.

2.1.2 Cytosolic pH-responsive polymeric nanomedicine

Nanoparticles could be taken up by cells through the endocytic pathway [47]. These nanoparticles must overcome endosomal trapping to release cargo into the cell cytosol. In particular, nucleic acids like small interfering ribonucleic acid (siRNA) are insecure in acidic endosomal environments [48, 49]. To break through this barrier, Ling et al. developed a pH-responsive, point-source burst nanoscale coordination polymer (NCP) particle named CbP/siRNA against PD (siPD)-L1@Dig, which contains carboplatin (Carb), digitoxin (Dig), and siPD-L1 [50]. In their research, when under acidic conditions, NCP generate phosphate ions and the produced osmotic stress could rupture endosomal

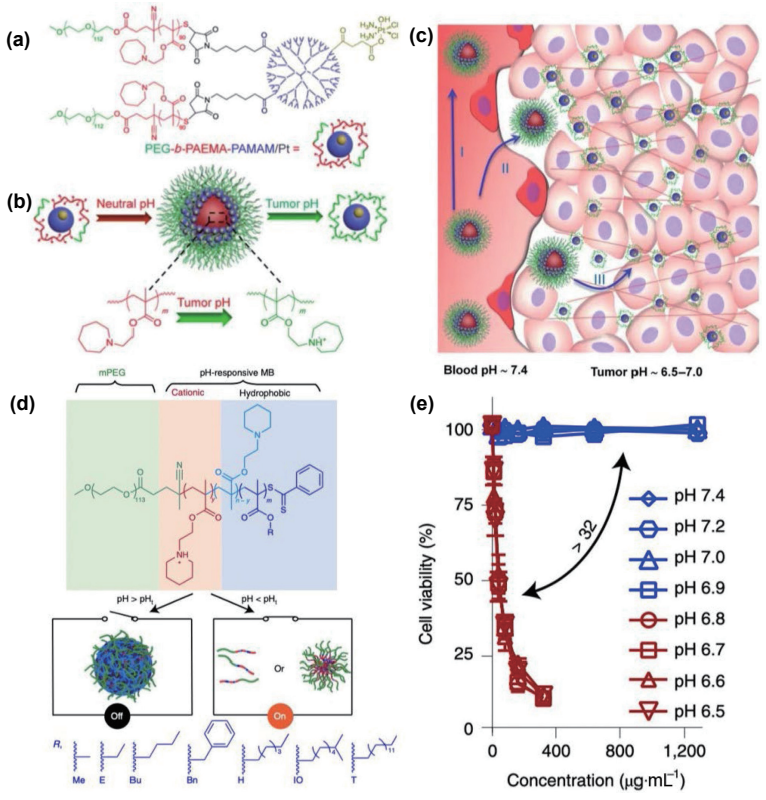

Figure 2 (a) Schematic illustration of the PEG-*b*-PAEMA-PAMAM/Pt structure. (b) PEG-*b*-PAEMA-PAMAM/Pt assembles into pH- SCNs/Pt at neutral pH. SCNs/Pt disintegrates into small particles at tumor acidic pH. (c) SCNs/Pt overcome biological barriers for precise drug delivery in poorly permeable pancreatic tumor models. Reproduced with permission from Ref. [44], © American Chemical Society 2016. (d) pTNTs exhibited a sharp state transition of membranolytic activity when going through a transition pH. (e) The cytotoxicity of P(C6-Bn20) at distinct pH after incubation. Reproduced with permission from Ref. [46], © Liu, M. D. et al. 2022.

membranes, allowing siPD-L1 for efficient endosomal escape. As a result, western blot analysis revealed that at a 5 nM siRNA dose, both CbP/siPD-L1 and CbP/siPDL1@Dig effectively suppressed PD-L1 expression, achieving knockdown efficacy of > 95% *in vitro*. Furthermore, CbP/siPD-L1@Dig dramatically inhibited tumor development in CT26-bearing mice, with a tumor growth inhibition (TGI) of 80.8% ± 5.6%, and mice showed a median survival of 44 days and less peritoneal metastatic dissemination.

Recently, increasing attention has been paid to the stimulator of interferon genes (STING), a cytosolic pattern recognition receptor that is crucial for eliciting spontaneous antitumor T-cell immunity [51, 52]. 2′ ,5-3′ 5′ cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) is an endogenous ligand for STING and is produced by the enzyme cyclic-GMP-AMP synthase in response to the existence of tumor-derived DNA in the cytoplasm [53–55]. T cells are primed by activating STING, initiating a complicated type I interferon (IFN-I)-driven inflammatory response [56]. However, cGAMP is restricted by its low bioavailability which hinders its access to the cytosol to engage with STING [57]. To solve this dilemma, Shae et al. developed polymersomes that contain an aqueous center and a vesicle membrane composed of pH-responsive, membrane-destabilizing amphiphilic diblock copolymer chains to realize its intracellular release and endosomal escape (Figs. 3(a) and 3(b)) [58]. Importantly, a molar ratio of cationic 2-(diethylamino) ethyl methacrylate (DEAEMA) groups to hydrophobic butyl methacrylate (BMA) moieties was previously revealed for the optimum of endosomal escape. As a result, they observed a 5–10 fold gene expression increase in mice treated with STING-nanoparticle (NP) in comparison with free cGAMP, along with a 35-fold increase of Cxcl1 and a 20-fold rise of Ifna2. Meanwhile, by utilizing B16F10 melanoma models, they revealed that STING-NPs achieved an 11-fold inhibition of tumor growth and a remarkable prolongation in the survival time compared to the cGAMP group. To go further, Shae et al. combined STING agonist with antigenic peptides as a personalized cancer vaccine, termed as NanoSTING-vax (Fig. 3(c)) [59]. This NanoSTING-vax elicited nearly 8% tumor-specific $CD8^+$ T cells in the blood, twice as much as in the free peptide group and the soluble mixture of cGAMP and peptide group.

Given the above, many pH-responsive polymeric nanomedicines were developed in the past few years. The upcoming direction of pH-responsive polymeric nanomedicine in cancer treatment may need to step towards the concept of "library", such as classification for different subtypes, causes, and stages of same cancer, and classification for different cancer types. Of course, this requires a large enough number of trials and samples.

2.2 Redox-responsive polymeric nanomedicine

Due to the fact that altered levels of redox molecules are closely related to numerous diseases, redox-responsive polymeric nanomaterials (PNMs) are appealing targets for DDSs [60]. In comparison with normal cells, tumor cells have a highly reducing environment due to the excessive GSH synthesis inside the cell [61]. In addition, tumor cells can produce excessive ROS, resulting in an increase in oxidative stress [62]. Based on the unique intracellular and extracellular redox environments of tumors, an increasing number of redox-responsive polymeric systems were created [60]. In this part, we discuss anticancer drug delivery polymeric systems including GSH-responsive and ROS-responsive in the past few years and highlight recent novel strategies.

2.2.1 GSH-responsive polymeric nanomedicine

Although neutral and negatively charged nanoparticles can travel further in the bloodstream in comparison with those positively

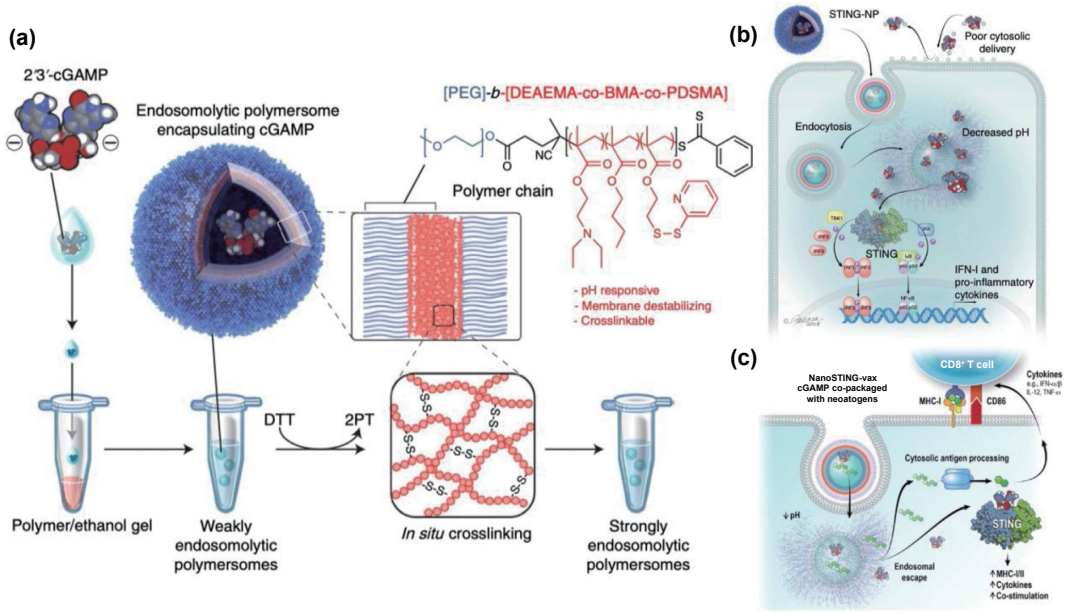

Figure 3 (a) Schematic illustration of the structure of the STING-NP and the strategy for augmenting the intracellular delivery of 2′3′-cGAMP. (b) STING-NPs increase the intracellular uptake of cGAMP. When exposed to the decreased pH within the endosomal environment, they advance the endosomal escape of cGAMP. Reproduced with permission from Ref. [58], © Shae, D. et al. 2019. (c) NanoSTING-vax enables the uptake of peptides and cGAMP by antigen presenting cells and could also facilitate cytosolic co-delivery of neoantigenic peptides and cGAMP through endosomal escape. Reproduced with permission from Ref. [46], © Liu, M. D. et al. 2022.

charged nanoparticles, their cellular absorption and tumor accumulation capability are restricted [63]. Alternatively, positively charged nanoparticles can assist endosomal escape and give rise to an enhanced tumor accumulation of therapeutics [64]. To address this issue, Jia et al. developed a GSH-responsive nanocarrier, which was composed of disulfide-doped organosilica-micellar hybrid nanoparticles. Also, the nanoparticles were modified with PEG and polyethyleneimine (PEI) (Fig. 4(a)) [65]. In this study, PEG shielded the positive charges of PEI and therefore prolonged the circulation of the nanocarrier via inhibiting the nonspecific protein adsorption. When the nanoparticles reach the TME, the extracellular GSH (2–20 μM) could induce the first-stage redox responsive activity, along with PEG chain separation. Then, the short-chain PEI was exposed to the environment and the nanocarrier carried positive charges, resulting in increased uptake of tumor cells via electrostatic interactions. Furthermore, owing to the proton sponge effect, the exposed PEI further promoted the endosomal escape of the nanocarrier and their entry into the cytoplasm [66, 67]. After that, high intracellular GSH concentrations could trigger second-stage redox responsiveness via disulfide bond breakage in the silsesquioxane matrix, resulting in the release of the inner drugs. Consequently, exploiting hydroxycamptothecin (HCPT) as a model drug, HCPT@DOSN-PEI-SS-PEG exhibited 2.5-fold improved antitumor efficacy (56.8%) in comparison with HCPT@DOSN-PEI-SC-PEG (23.0%).

Besides, conjugating two drugs to generate a dimeric prodrug is a promising method for achieving the combinatory therapeutic efficacy of both drugs. Previously, researchers demonstrated that using a dimeric prodrug can boost the efficiency of drug encapsulation and improve the loading stability by increasing the hydrophobic contact between drug molecules [68]. Also, the linkage between two drugs can be responsive to the redox state, such as the disulfide bond, which allows the drugs to be released in a specific environment. For example, Liu et al. developed a GSH-responsive prodrug that not only inhibit glycolysis of tumor cells but also reverse the immunosuppressive microenvironment (Fig. 4(b)) [69]. In this study, lonidamine (LND) and NLG-919 were connected by a disulfide bond and were loaded in F127 micelles (donated as LSN@F127). After tumor cells uptaked the nanoparticles, the overexpressed GSH could cleave disulfide bonds and promote the drug release. The released LNDs further engaged with mitochondria and reduced HK II expression, therefore interfering with tumor cell glycolysis [70]. Meanwhile, the levels of ROS were considerably increased as a result of LND activation and disulfide bond consumption of GSH, which efficiently killed tumor cells through immunogenic cell death (ICD), prompting a subsequent immunological response. Combinatory use of NLG919 could alleviate tumor immunosuppressive microenvironment and thus dramatically suppress tumor growth. As a consequence, compared to the single drug, the produced dimeric prodrug could significantly boost drug loading effectiveness in F127 micelles.

Recently, adjuvant therapy such as injecting supportive cytokines (such as interleukins) or TME modulating substances, are frequently applied to improve the therapeutic potency of adoptive transfer of tumor-specific T cells (ACT) [71, 72]. Regarding that systemic administration of immunomodulators might bring adverse events, delivering adjuvant agents to the ideal place is of necessity [73]. In the previous work of Irvine's group, they presented an alternative chemistry-based strategy to deliver adjuvant drugs during adoptive treatment by attaching the drug-loaded lipid nanoparticles (dubbed "backpacks") to the plasma membrane of T cells *via* their surface thiol groups [74, 75]. To further increase the controllability and efficiency of the drug release, they developed a strategy for chemically coupling adjuvant delivery and T cell activation using TCR-responsive nanoparticle backpacks [76]. Further in their research, they noticed that the reinforced redox activity on the primed $CD8^+$ T cell surface could be used to induce adjuvant release in response to antigen stimulation. Accordingly, they synthesized a bis-N-hydroxy succinimide (NHS) cross-linker containing a disulfide bond (NHS-SS-NHS) and determined the conditions under which the solution–phase interaction of the cross-linker and cargo proteins could induce the formation of nanogels (NGs) (Fig. 4(c)). As a result, the disulfide bond was engineered to be cleaved in response to the reducing conditions like high GSH concentrations around the T cell surface, inducing the protein cargo release. Adopting

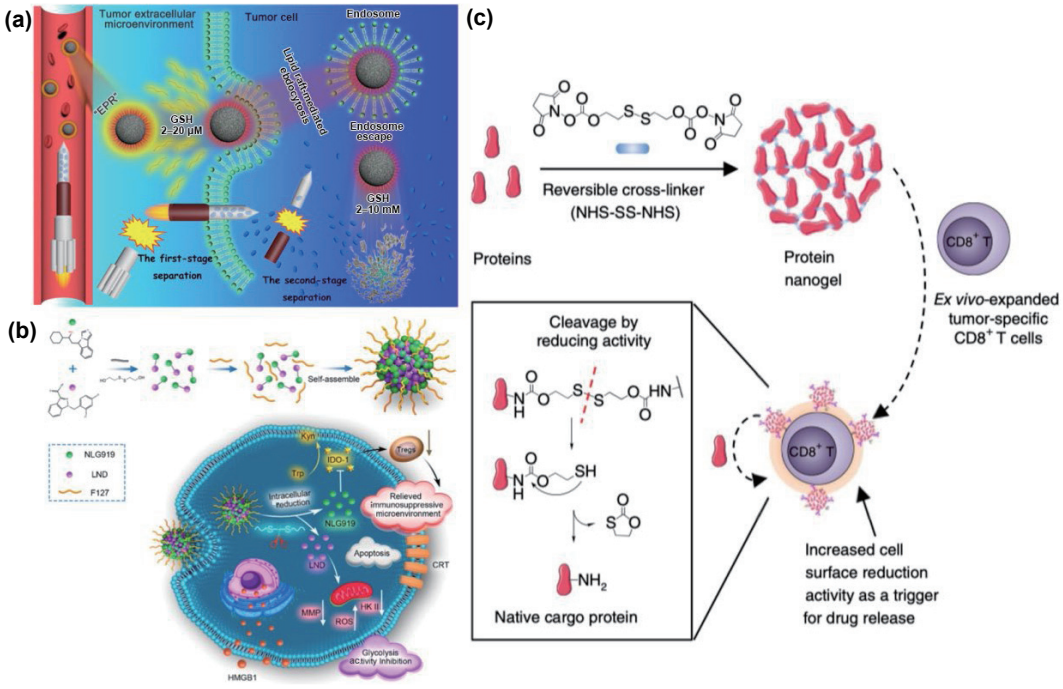

Figure 4 (a) The rocket-mimetic mechanism of DOSN-PEI-SS-PEG drug nanocarrier. Reproduced with permission from Ref. [65], © American Chemical Society 2019. (b) The GSH-responsive dimeric prodrug can restrain the glycolysis and alleviate the immunosuppressive microenvironment to suppress tumor growth. Reproduced with permission from Ref. [69], © American Chemical Society 2021. (c) Schematic illustration of protein NG synthesis. Such NG can respond to the reducing local microenvironment for promoting drug release. Reproduced with permission from Ref. [76], © Nature Publishing Group, a division of Macmillan Publishers Limited 2018.

human IL-15 superagonist (IL15Sa) as a tested drug cargo, they discovered that T cells packed with T-cell receptor (TCR)-responsive NGs exhibited a 16-fold increase of proliferation in tumors than T cells driven by systemic cytokine administration. Moreover, this controlled release enabled an 8-fold increase in dosage limit compared to the free cytokine.

2.2.2 *ROS-responsive polymeric nanomedicine*

Numerous responsive DDSs based on the variance of ROS have been created to provide precise drug delivery to the disease lesions [77–79]. However, the short lifetime, narrow diffusion, limited effect range, and restricted intracellular ROS level severely impede their treatment efficacy [80, 81]. Meanwhile, mitochondria takes a critical part in supplying cellular energy and inducing apoptosis [82]. Also, it is possible to generate large concentrations of mitochondrial ROS (mtROS) *in situ* and damage mitochondria, triggering programmed cell death [83, 84]. Therefore, drug delivery methods that target mitochondria with ROS responsiveness were developed to increase efficacy and minimize the possible side effects. For instance, Zhang et al. developed a ROS-responsive nanocarrier with dual-targeting properties toward tumor cells and intracellular mitochondria, exhibiting self-circulation of mitochondrial drug release with a burst of mtROS for enhanced cancer therapeutic efficacy [85]. In their study, the dual-targeted polymeric nanoparticles were composed of ROS-responsive camptothecin (CPT) prodrug monomer with a thioketal bond (DT-PNs) (Fig. 5(a)). The increase of mtROS in tumor cells could induce the release of CPT in mitochondria. *In situ* produced CPT further stimulated the circulation of mtROS, resulting in the further high-dosage release of CPT and a final burst of mtROS, both of which were capable of eliciting enduring high-oxidative stress and achieving efficient cancer cell elimination. As a result, the apoptotic ratio of DT-PNs group (45.73%) was substantially greater than CPT group (34.27%). And the *in vivo* test showed that DT-PNs achieved an 81% tumor inhibition ratio.

In the article discussed above [69], the GSH-responsive prodrug could achieve great therapeutic efficacy for tumor treatments. However, compared with this redox-responsive strategy, a ROS-responsive method is more tumor-specific and holds great promise to expand the exposure of tumor cells toward prodrugs due to the fact that the GSH concentrations between tumor cells and normal cells present insignificant variation [86–88]. For example, Xu et al. chose the anticancer drug mitoxantrone (MTO) and created a ROS-responsive MTO-based polyprodrug (iRGD-NPs). Mechanistically, MTO was copolymerized with a ROS-cleavable thioketal-containing linker to form the polyprodrug, termed as polyMTO (Fig. 5(b)) [89]. The presence of ROS in tumor cells could induce the thioketal link break in the polyMTO, leading to the programmed release of intact MTO for interrupting DNA synthesis. As a consequence, the group treated with iRGD-NPs achieved superior therapeutic efficacy compared to free MTO.

Moreover, tumor cells have a significant level of heterogeneity of redox potential [90]. The overproduced ROS and GSH vary in different types of tumor or in distinct locations within the same type of tumor. In addition, the fluctuation levels of GSH and ROS have been observed at distinct stages of tumor growth [90]. However, the mainstream of stimuli-responsive nanoparticulate DDSs were supposed to respond to either ROS or GSH, leaving limited therapeutic efficacy. Luo et al. expected that a single thioether could be more efficient as a dual-sensitive linkage than a dithioether. To verify their hypothesis, they devised and produced two new redox dual-sensitive PTXfatty acid conjugates (PTX-S-OA and PTX-2S-OA) by conjugating oleic acid (OA) to paclitaxel (PTX) through a single thioether bond or a dithioether bond respectively (Fig. 5(c)) [91]. Furthermore, the PTX-S-OA was significantly more superior than the PTX-2S-OA in the matter of tumoricidal potency. This work may explore the future avenue of redox dual-sensitive DDSs for achieving enhanced therapeutic efficacy.

On the whole, it is discovered that combination therapy shows a potential development direction for redox-responsive polymeric

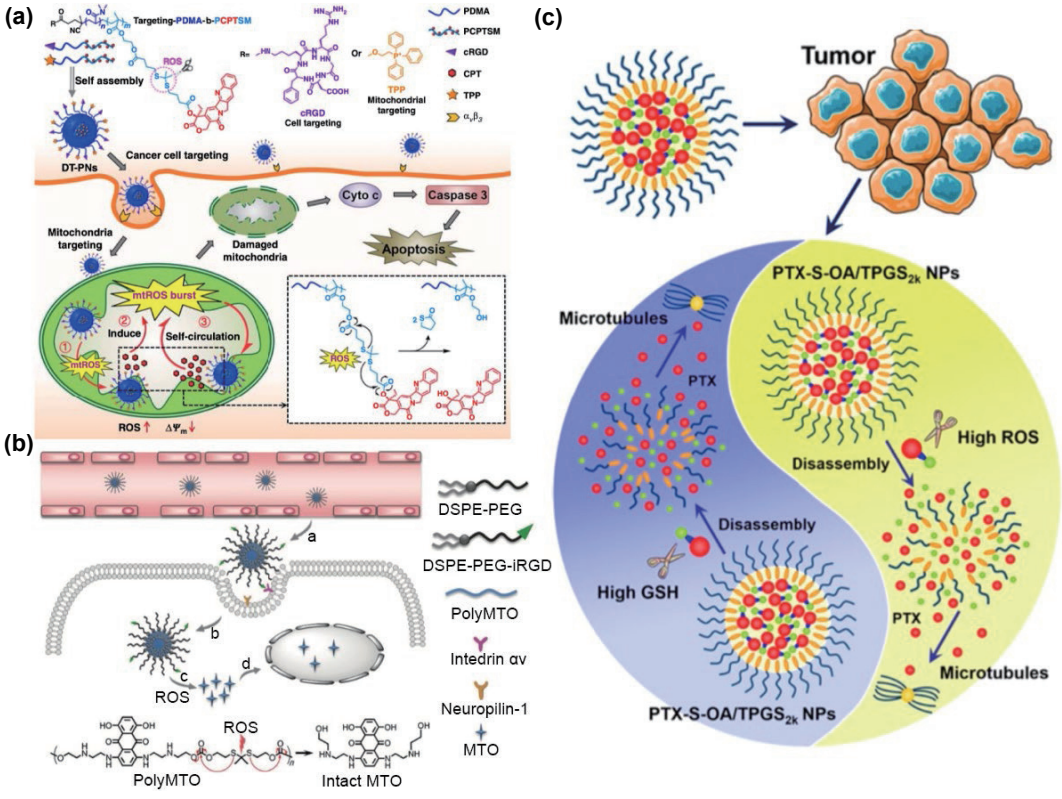

Figure 5 (a) Schematic illustration of mitochondria-target polyprodrug for self-circulation release of CPT and the burst of ROS level. Reproduced with permission from Ref. [85], © Zhang, W. J. et al. 2019. (b) The polyMTO-based NP platform can target and deeply penetrate tumor tissues for cancer treatments. Reproduced with permission from Ref. [89], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2017. (c) The redox dual-responsive drug release of prodrug NPs that can respond to the opposite stimuli within tumor cells. Reproduced with permission from Ref. [91], © American Chemical Society 2016.

platforms in cancer treatment. The combination includes different treatments and multiple stimulus. In order to achieve enhanced efficacy, how the redox response interacts with various stimulus such as redox-pH and redox-enzyme needs to be more deeply learned. For example, diselenide bonds have a special dual redox response that may respond to both oxidants and reductants simultaneously.

2.3 Enzyme-responsive polymeric nanomedicine

The enzyme-responsive nanoplatform is also often developed for achieving precise drug delivery [92]. TME is enriched with various enzymes. Most malignant tumor cells express a high level of gelatinase-A (MMP-2), gelatinase-B (MMP-9), and esterase which can be exploited as the trigger [93, 94].

2.3.1 MMP-responsive polymeric nanomedicine

MMP is a family of extracellular proteinases that degrade various proteins [95]. Among them, MMP-9 and MMP-2 are frequently overexpressed in malignant cancers such as breast cancer, pancreatic cancer, and lung cancer. They are tumor cell growth regulators and take a vital part in angiogenesis at the tumor site. Besides, other members of the MMP family, like MMP-12 and MMP-13, are highly expressed in lung cancer, and MMP-3 is found to put forward the development of breast cancer. The close relationship with tumorigenesis in the TME renders MMP a suitable target for designing responsive polymeric nanomedicine.

For instance, Cassandra et al. invented a general MMP-responsive nanoparticle to achieve the precise drug release in tumor sites [96]. This polymeric nanomedicine was synthesized through diblock copolymerization. PTX and MMP-responsive peptides were covalently linked to norbornene analogs monomers and copolymerized through ring-opening metathesis polymerization. PTX acted as the hydrophobic moiety of the polymer via a biodegradable ester and MMP substrate peptide functioned as the hydrophilic block. The polymer was capable of self-assembly into nanoparticles upon dialysis from dimethyl sulfoxide (DMSO) against aqueous solution. The MMP-responsive nanoparticle underwent dramatic morphology change within the TME as a consequence of MMP degradation of its peptide shell, and further released paclitaxel into the tumor cell via hydrolysis (Fig. 6(a)). The nanoparticle with a great drug loading capability (63% by weight per polymer) exhibited improved biosafety and tumor inhibition efficacy. The maximum tolerated dose of the MMP-responsive nanoparticle (240 mg/kg in the mouse model) was 16 times higher than clinical PTX without overt toxicity. In the HT1080 xenograft model, efficacy was examined among responsive nanoparticles, non-responsive nanoparticles, and clinical PTX. At the dose of 15 mg/kg, the responsive nanoparticle exhibited slightly stronger inhibition than the non-responsive type. Moreover, scientists have developed MMP-2 and MMP-9 specific responsive units to target TME. For example, Han et al. engineered MMP-2 sensitive polymeric nanomedicine that enhanced drug penetration into solid tumors (Fig. 6(b)) [97]. The monomer consists of a hyaluronic acid (HA) protective shell, amidogen of PAMAM core, and an MMP-2 cleavable peptide. They were linked via click reaction to form an HA-peptide-PAMAM macromolecule. And doxorubicin was incorporated within the PAMAM core. Upon MMP-2 degradation, the nanoparticle could precisely release its payload within the TME. This strategy showed an improvement in tumor growth inhibition of nearly 50% more than merely doxorubicin solution while alleviating systematic toxicity. Similarly, Gordon et al. created an MMP-9 responsive nanogel to increase tumor-specific cellular uptake (Fig. 7(a)) [98]. The outer layer of the polymer nanogel was covered with PEG-conjugated MMP-9 responsive peptide. Upon exposure to MMP-9, the PEG shell could degrade and the inner core was exposed. The positive charge-bearing polyamine-type surface therefore rapidly entered

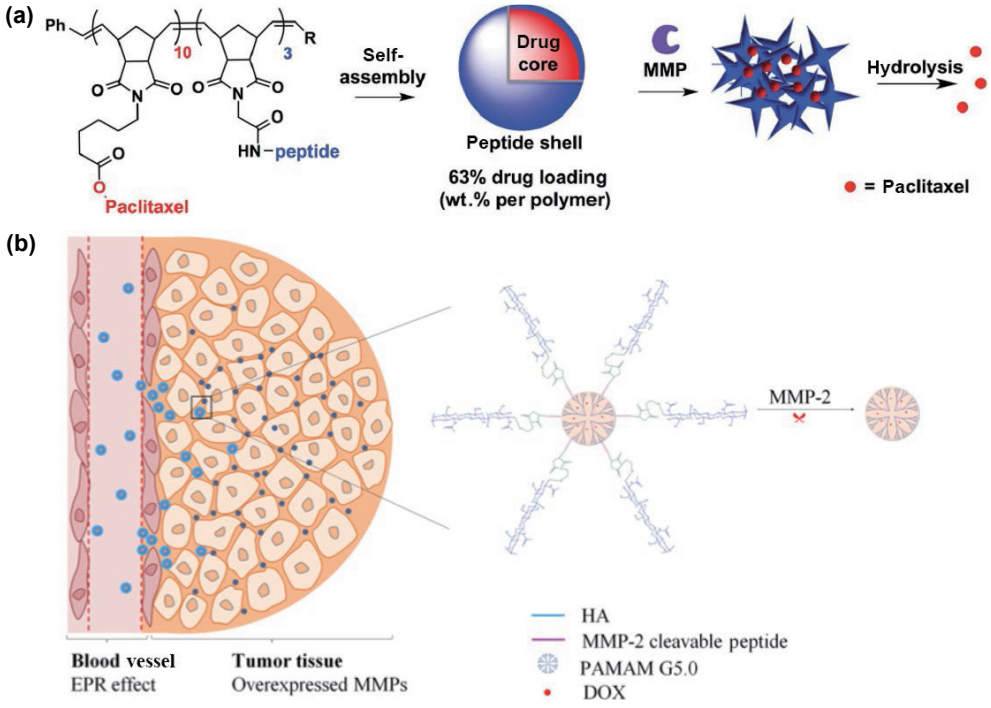

Figure 6 (a) Paclitaxel and MMP-responsive peptide are copolymerized to generate responsive nanoparticles. Extracellular MMP would cause disintegration of the polymer and release PTX. Reproduced with permission from Ref. [96], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2015. (b) The protective hyaluronic acid shell of the MMP-2 responsive-polymeric nanomedicine would be removed upon MMP2 exposure, and doxorubicin will be released within the TME. Reproduced with permission from Ref. [97], © American Chemical Society 2017.

into the tumor cells, and the nanogel further released a noncovalent payload within cells. The MMP-9 responsive peptide decorated nanoparticle exhibited nearly 10 times of the cellular uptake of naked nanoparticles.

2.3.2 *Esterase-responsive polymeric nanomedicine*

Esterase is an intracellular enzyme, usually overexpressed in malignant tumors, such as in colorectal tumor [94]. Their high expression is intimately connected to the promotion of tumor growth and migration. Esterase's ability to catalyze the hydrolysis of various ester bonds is promising for liposome dissociation and cleavage of drug–drug conjugate via an ester bond. For polymeric nanomedicine, utilizing esterase to reverse carrier charge or degrade protective shell are emerging applications of esterase-responsive units.

Qiu et al. designed an esterase-responsive nanomedicine for gene therapy to target tumor while avoiding fibroblast hyperactivation (Fig. 7(b)) [99]. The polymer core was protected from extracellular esterase degradation via a 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE) lipid and cholesteryl 3β-N-(dimethylaminoethyl) carbamate shell. Since esterase is overexpressed in cancer cells, the peripheral quaternary amines with N-propionic 4-acetoxybenzyl ester substituents quickly disassembled and released DNA due to charge conversion. However, such polymeric nanoplatform remained as unchanged cationic because of the lack of esterase in fibroblasts. Consequently, selective apoptosis of tumor cells was induced as plasmid encoding apoptosis-inducing ligand was delivered into the nucleus. The efficiency of this therapy was examined in an intra-peritoneal cervical tumor model. Such polymeric nanomedicine dramatically decreased the number of tumor nodules than common chemotherapy drugs including PTX, cisplatin, and irinotecan. WNT16B, a fibroblast hyperactivation signal, was found downregulated in comparison with chemotherapy, indicating its selectivity. Similarly, Saw et al. developed an esterase-responsive polymer-prodrug for siRNA delivery, which allowed the nanoplatform to release its payload in tumor cells [100].

Besides its application for gene therapy, esterase-responsive units were also applied to deliver small molecules. In a recent study by Sui et al., natural product triptolide (TPL) was linked to the PDA-polyethylene glycol (PDA-PEG) polymer via an ester bond to avoid its systematic toxicity and improve its solubility (Fig. 8(a)) [101]. The polymer self-crosslink with PDA-PEG-lactobionic acid to form nanoparticles. Lactobionic acid was exposed to the outer layer of the nanoparticle to interact with β-D-galactose receptors, which encouraged endocytosis by cancer cells. Subsequently, the linkage of polymer and TPL was cleaved through esterase degradation to reach the tumoricidal effect.

2.3.3 *Gamma-glutamyl transpeptidase (GGT)-responsive polymeric nanomedicine*

GGT is a type of membrane enzyme responsible for the transfer of a γ-glutamyl group to acceptor peptides and amino acids [102]. They could mediate transcytosis between densely packed cells, such as epithelial and endothelial cells in the lung, liver, and vascular systems. With their highest intracellular concentrations in the liver, they are regarded as sensitive biomarkers for liver pathologies [103]. As for nano-based strategy design, hijacking GGT to attain augmented drug penetration into tumor cells is a rising interest for nanoscientists.

To trigger GGT-mediated transcytosis, Zhou et al. designed a GGT-responsive zwitterionic polymeric nanocarrier to achieve deep penetration into the tumor cells (Fig. 8(c)) [104]. Adsorption-mediated transcytosis (AMT) could be encouraged efficiently by the cationization of nanoparticles [105]. The drug-conjugate PBEAGA-CPT produces primary amine through GGT-catalysed γ-glutamylamide hydrolysis, thus leading to a quick transcytosis and endocytosis and consequently enhancing the tumor penetration and therapeutic efficacy. Similarly, Wang et al. developed a GGT-responsive dendrimer-drug conjugate to achieve deep penetration into the liver tumor (Fig. 8(b)) [106]. GSH was selected as the GGT-responsive unit for its superior activity as a GGT substrate, and CPT was connected to the poly-amidoamine dendrimer via a ROS-sensitive thioketal linker. The

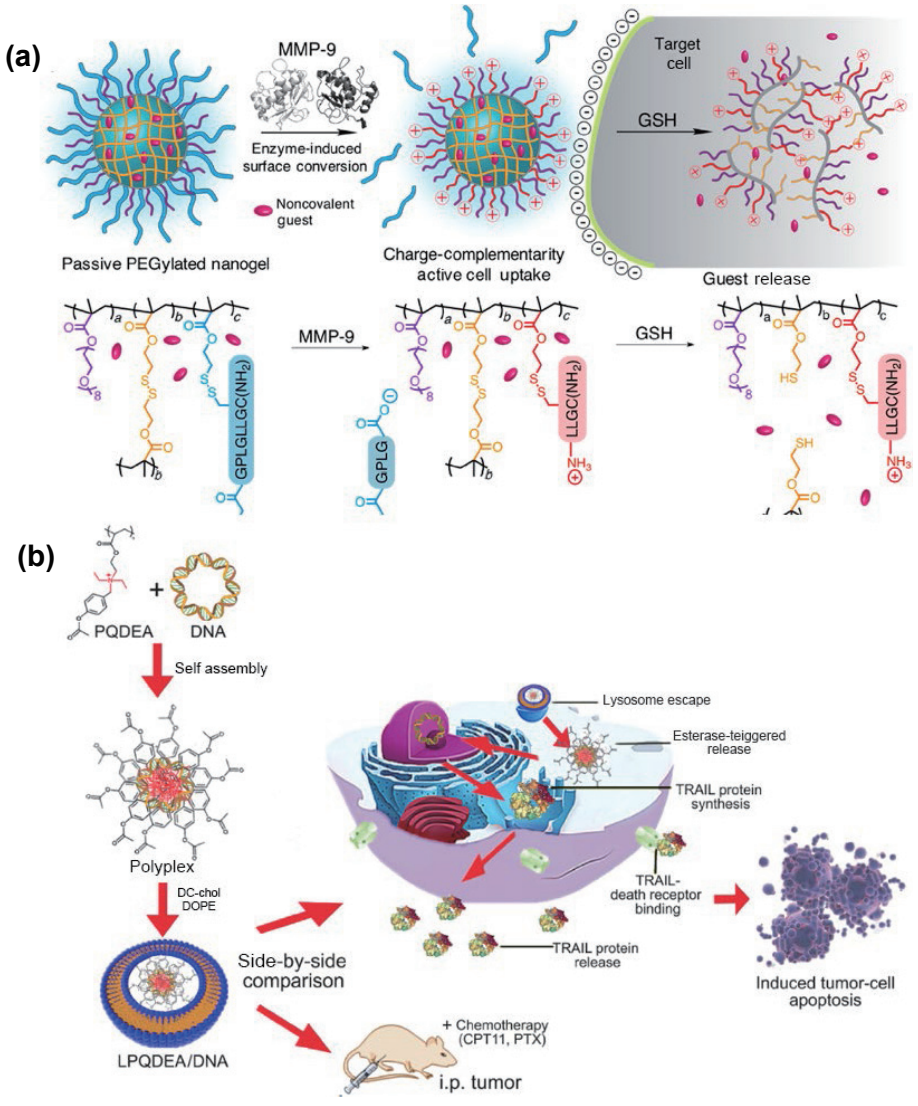

Figure 7 (a) The outer layer of the PEG chain on MMP-9 responsive polymeric nanomedicine will be cleaved in the TME, leading to the charge reversal of the nanoparticle. The nanoparticle would enter the tumor cell via transcytosis and realize its therapeutic purpose. Reproduced with permission from Gordon et al. [98], © American Chemical Society 2018. (b) Esterase-responsive polymeric nanomedicine assisted gene therapy drug for intracellular release. Reproduced with permission from Ref. [99], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2016.

outer layer of GSH could be recognized by GGTs on the vascular endothelial cells and degraded into the positive-charged polymer, allowing caveolae-mediated transcytosis for the nanoparticles delivery into TME. GSH-modified dendrimer achieved substantial inhibition of xenograft BxPC-3 tumors, while PEG-modified analogs still resulted in seven times increase of the tumor volume, suggesting the significance of the GGT-responsive mechanism on therapeutic efficacy.

As has been noted, most of the available enzyme-responsive polymeric delivery platforms are still in the proof-of-concept (POC) stage [107]. These platforms need to undergo additional biosafety testing including assessments of their immunogenicity, toxicity, pharmacokinetics, and biocompatibility before they may be potentially translated into clinical use.

3 Other bioresponsive materials for various diseases

Apart from pH-, redox-, and enzyme-responsive nanomedicines, bioresponsive materials are available in a wide range of various types and are employed in many diseases. When developing bioresponsive materials for disease treatments, endogenous variations are appealing targets since they are frequently significant markers for several sorts of diseases [108–110]. Meanwhile, other typical endogenous stimuli include glucose, ions, adenosine triphosphate (ATP), hypoxia, mechanical cues, as well as nucleic acids [111]. For example, to enable on-demand cargo release, the ATP-controlled DDSs usually employ ATP-targeted aptamers as mediums [112]. To be specific, ATP either drives conformational changes that produce structure-disorder forces or competitively binds to loading sites of cargo to initiate release. Based on these unique functions of ATP, there are many studies about ATP-controlled formulations in the past few years, including tubular structure, poly-ion micelles, aptamer-crosslinked DNA microcapsules, nanogels composed of DNA complexes, and silica [113–117]. More functions and types of different ATP-responsive materials and DDSs can be referred to Deng's review [118].

4 Conclusions and prospects

In this review, recent advances of bioresponsive polymer for cancer treatment are highlighted. With the rapid advancement of nanotechnology, diverse multifunctional agents at the nanoscale can be effectively synthesized. Polymers, in particular, have shown great potential in cancer immunotherapy and chemotherapy, as well as in their application as drug solubilizers and stabilizers.

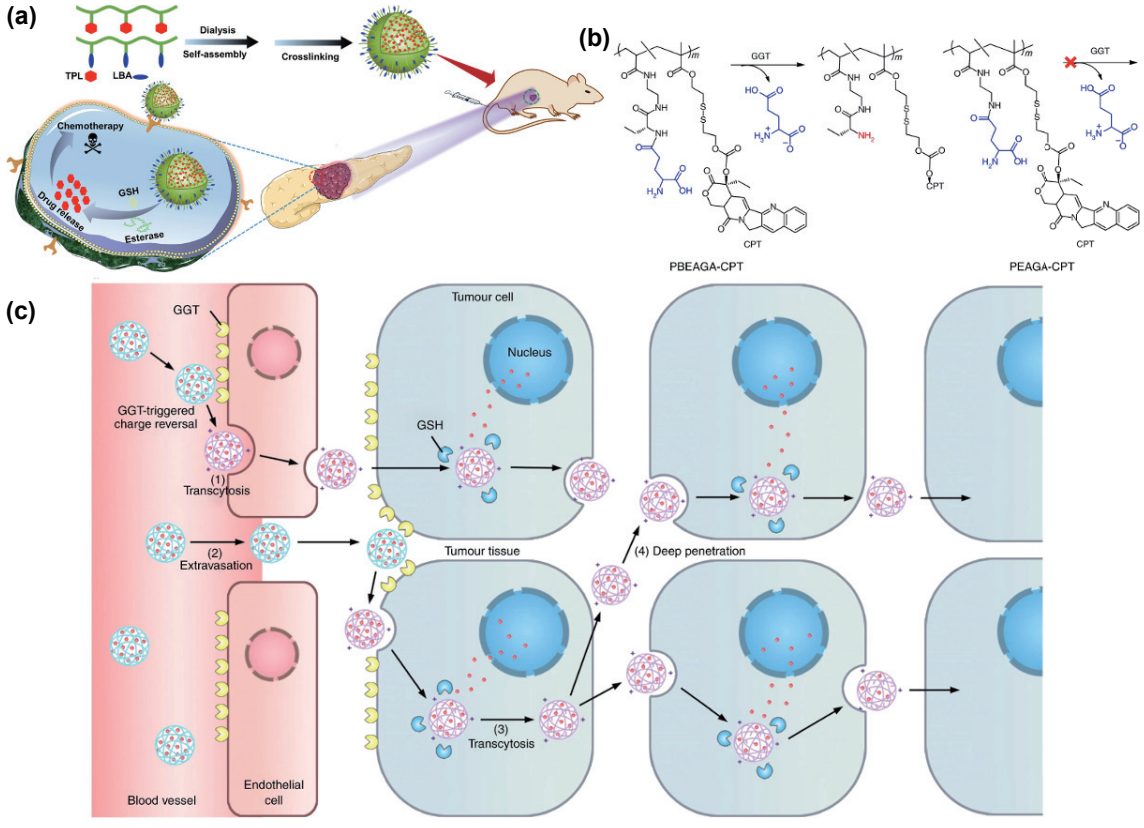

Figure 8 (a) Esterase-responsive polymeric nanomedicines achieved precise delivery of TPL into tumor cells to attenuate systematic toxicity. Reproduced with permission from Ref. [101], © Sui, B. L. et al. 2021. (b) The structure of PBEAGA-CPT and PEAGA-CPT, and PBEAGA-CPT can produce primary amine through GGT-catalysed γ-glutamylamide hydrolysis. (c) GGT-responsive dendrimer achieved deep penetration into tumor to improve therapeutic efficacy. Reproduced with permission from Ref. [104], © Zhou, Q. et al. 2019.

Bioresponsive polymers could enable more sophisticated control and realization of precise and efficient release by exploiting endogenous physiological properties as triggers. Such design facilitates the precise release of chemotherapeutic and immunotherapeutic agents at the specified tumor sites, offering the feasibility of specific and precise treatments.

Despite the significant progress made in this field, bioresponsive polymers must overcome certain barriers before clinical translation. First, the pH and redox state of tumors are often variable rather than constant in tumor cells, which may result in the false activation of such bioresponsive nanosystems. To solve this problem, a more sensitive bioresponsive polymer needs to be developed. For example, Liu et al. synthesized a P(C6-Rx) library to obtain the most sensitive pH-responsive material by screening the whole library [46]. Likewise, Chen et al. reported a pH-activatable nanophotosensitizer library that could be utilized to spatiotemporally target different phases of endosomal maturation, thus inducing adjustable cellular pyroptosis [119]. This kind of bio-signal amplification response components and library screening opens the future avenue for improvements. Furthermore, further knowledge of tumor biochemical properties is required to assist the design of bioresponsive polymers with augmental efficacy. Second, the bioresponsive polymer must be stable within the body's circulation before reaching the tumor site. To accomplish this, Jia et al. created multi-stage responsive polymers. They synthesized a gradient redox-responsive and two-stage rocket-mimetic drug delivery system allowing longer blood circulation and improved tumor accumulation [65]. Third, as new biological characteristics of cells and cytokines are being discovered, it is important to assess the targetability of cells within the TME in order to identify potential targets for polymeric nanomedicine. For instance, Tang et al. aimed tumor-associated neutrophils with enzyme-responsive polymers through its specific enzyme myeloperoxidase (MPO) [120], indicating an innovative therapeutic strategy for immune modulation in TME. As an extension, the bioresponsive DDSs are not limited to cancer immunotherapy and chemotherapy. Moreover, response targets can be generalized and applied to other materials. Overall, by the incorporation of interdisciplinary technologies and personalized analytical tools, bioresponsive polymers have a significant clinical impact for precision medicine with enhanced efficacy and limited side effects.

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