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Review

Stimuli-responsive prodrug-based cancer nanomedicine

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ABSTRACT

The rapid development of nanotechnology results in the emergence of nanomedicines, but the effective delivery of drugs to tumor sites remains a great challenge. Prodrug-based cancer nanomedicines thus emerged due to their unique advantages, including high drug load efficiency, reduced side effects, efficient targeting, and real-time controllability. A distinctive characteristic of prodrug-based nanomedicines is that they need to be activated by a stimulus or multi-stimulus to produce an anti-tumor effect. A better understanding of various responsive approaches could allow researchers to perceive the mechanism of prodrug-based nanomedicines effectively and further optimize their design strategy. In this review, we highlight the stimuli-responsive pathway of prodrug-based nanomedicines and their anticancer applications. Furthermore, various types of prodrug-based nanomedicines, recent progress and prospects of stimuli-responsive prodrug-based nanomedicines and patient data in the clinical application are also summarized. Additionally, the current development and future challenges of prodrug-based nanomedicines are discussed. We expect that this review will be valuable for readers to gain a deeper understanding of the structure and development of prodrug-based cancer nanomedicines to design rational and effective drugs for clinical use.

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1. Introduction

Currently, with the significant advancement of nanotechnology, a variety of nanomedicines have been developed and introduced into the field of cancer treatment, including inorganic nanocrystals [1], polymer nanoparticles [2], biomimetic nanomaterials [3], and nanohybrids [4]. Most of the common nanomedicines incorporate nanocarriers such as nanoMOFs [5], 2D nanosheets [6], and nanogels [7] as anticancer drug-delivery nanoplatforms for oncotherapy. Typically, most of the nanomedicines, especially drug delivery nanoplatforms, suffer from the bottlenecks of low efficiency, serious side effects, and limited target efficiency to tumor tissues, which usually limit clinic translation potential. To overcome these disadvantages, the stimuli-responsive nanomedicine has been developed to precisely release drugs at specific sites for noninvasive cancer therapy [8]. Prodrug based nanomedicines are one of the typical representatives of stimuli-responsive nanomedicines that controllably release drug under external stimulations.

The prodrug (drugs conjugated to the precarrier), an inactive compound that can be enzymatically degraded into the parent bioactive drug in vivo, has gained wide attention as a practical approach to reduce off-target toxicity in cancer treatment. Due to its unique structure, most prodrugs can self-assemble into nanoparticles through simple chemical modifications. The prodrug exhibits several significant advantages, including high drug loading efficiency, ameliorative drug availability, drug release controllability, and less tendency to agglomerate after encapsulation [9]. Considering the different structures, prodrug-based nanomedicines can be classified into three categories: prodrug-based polymer conjugated nanomedicines, small molecular prodrug-based self-assembled nanomedicines, and prodrug-encapsulated nanomedicines.

Compared to other types of nanomedicines, the prodrug-based nanomedicines are able to cleverly and sensibly respond to certain stimuli and release the desired drugs. After decades of development, numerous prodrug-based nanomedicines with different chemical modifications have emerged as corresponding stimulus responsive, including the internal tumor microenvironment (TME) stimulus (e.g.,

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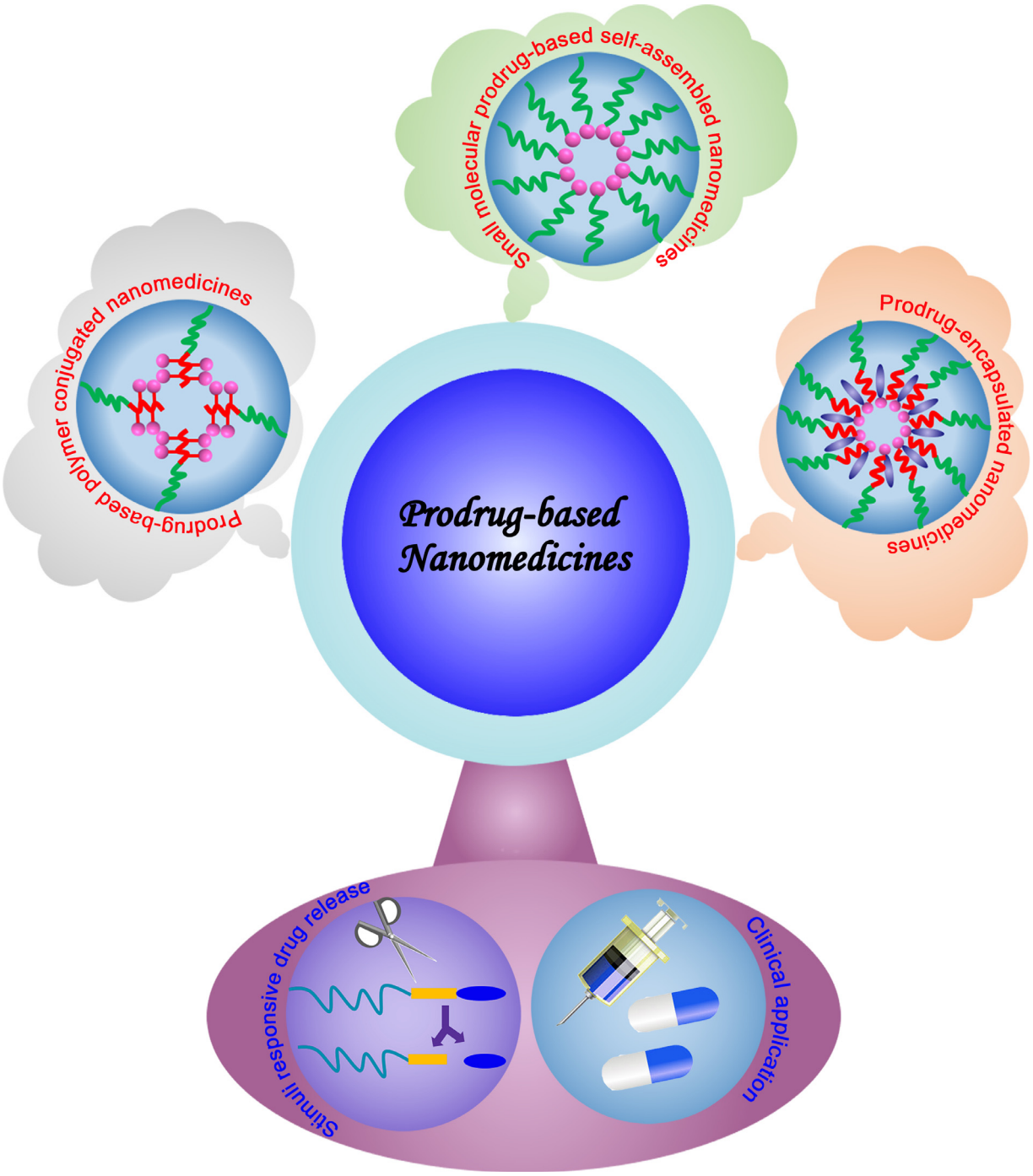
pH, redox environment, enzymes and hypoxic, etc.) [10–15] and the external environmental stimulus (e.g., light, thermo, ultrasound, and magnetism field, etc.) [16–18]. Most importantly, selecting the proper type of stimuli and chemical modifications in different situations are the key to design satisfying prodrug-based nanomedicines.

Although many reviews discuss the progress of prodrugs for cancer therapy, very few articles focus on the stimuli-responsive prodrug nanomedicines. This review will summarize essential aspects of stimuli-responsive prodrug nanomedicines in cancer therapy; including various types of prodrug-based nanoparticles, different stimulus, challenges, perspective, and recent advancement in clinical applications (Scheme 1). We expect this timely review article to provide deep insights into the development of stimuli-responsive prodrug-based nanomedicines for cancer therapy.

2. Types of prodrug-based nanomedicines

The types of prodrug-based nanomedicines mainly include, prodrug based polymer conjugated nanomedicines, small molecular prodrug-based self-assembled nanomedicines, and prodrug-encapsulated nanomedicines.

For prodrug-based polymer conjugated nanomedicine, drug molecules are usually covalently conjugated to polymers via chemical modifications to configure prodrug-based nanoparticles (NPs). Currently, conjugating drug molecules to the polymer scaffold is the most widely used approach to synthesize prodrug-based polymer nanomedicines. Various polymers, including hydrophilic polymer, hydrophobic polymer, and amphiphilic polymer, have been employed to synthesize polymer-drug conjugates for cancer therapy.



Scheme 1. Schemes of different types of prodrug-based nanomedicine and their stimuli-responsive pathways and applications in the field.

On the structural bases, the polymers are divided into three categories that are widely utilized to synthesize polymer-drug conjugates: (i) comb-like copolymers [19]; (ii) block copolymers [20]; and (iii) dendritic copolymers [21]. These copolymers have common advantageous characteristics such as: it contains numerous functional sites on the polymer skeleton, and anticarcinogen molecules are mainly cross-linked to the polymer as branched chains to achieve high drug loading efficiency. In addition, poly(ethylene glycol) (PEG) block copolymers, polypeptides [22], polysaccharides [22], and polyaminoacids [23] also contain a great deal of active functional groups such as carboxyl, amino, and hydroxyl which could be easily modified in chemical manner to form satisfying polymer-drug conjugates nanomedicines.

Another prodrug-based nanomedicine is the small molecular prodrug-based self-assembled nanomedicine. This kind of nanomedicine has the following characteristics: (i) the molecular weight of the nanocarrier is very low with a small nanostructure, (ii) the anticarcinogen regulates the hydrophilic and hydrophobic balance of conjugates. Different from polymer prodrugs, the small molecular prodrugs are usually obtained via cross-linking the molecule to another molecule. Subsequently, the small molecular prodrug would self-assemble into prodrug-based nanomedicines. Most of these nanomedicines mainly contain cyclodextrin−drug conjugates [24], pillararene-drug conjugates [25], amphiphilic peptidic prodrugs [26], and lipid drug conjugates (e.g., squalenoylations [27], cholesteryl [28], and unsaturated fatty acids [29] prodrugs) of anticancer agents. Additionally, though the small molecular prodrug-based self-assembled nanomedicines possess many advantages, including smaller size and higher drug loading efficiency, nevertheless, shortcomings such as short blood circulation life and poor structural stability can not be ignored. Therefore, an amphiphilic copolymer containing a long amphiphilic chain such as phospholipid polyethylene glycol (DSPE−PEG) is usually introduced and implemented to modify the small molecular prodrug self-assembled conjugates for prolonging the blood circulation time and improving the structural stability [30].

Prodrug-encapsulated nanomedicines is a special kind of nano-assembled prodrug, which mainly utilizes nanocarriers (e.g. inorganic NPs, liposomes, micelles or nanogels) to load or encapsulate anticancer prodrugs through a noncovalent binding. Benefiting from the merits of prodrug and nanoscience, the obtained prodrug-encapsulated nanomedicines have higher targeting efficiency, better drug utilization and less side effect [9]. Notably, for these kinds of nanomedicines, any suitable biological material can be selected as the carriers for prodrug delivery without additional restrictions. However, with no difference from the common drug delivery systems, the low drug loading efficiency still limits the clinical development of prodrug-encapsulated nanomedicines [31]. Although this prodrug strategy is not more significant as compared to the above mentioned two strategies, it has dramatically attracted more attention in recent years due to the unique advantage of no carrier restrictions.

3. Stimuli-responsive drugs release

This section will introduce the general stimuli-responsive drugs release classifications/types of prodrug-based nanomedicines, including endogenous stimuli and exogenous stimuli.

3.1. Endogenous stimuli

3.1.1. pH-responsive

The anaerobic glycolysis of the tumor cells results in the accumulation of the acidic metabolite, therefore the TME presents weak acidity feature. Rapid tumor growth leads to irregular angiogenesis, thereby causing a rapid depletion of both oxygen and nutrients. The glycolytic metabolism involved in this process results in the generation of acidic metabolites in the tumor stroma. Under this condition, numbers of prodrug-based nanomedicines with low pH-responsive polymer conjugates have been designed. The pH-sensitivity relies on the degradation of acid-cleavable linkers or the protonation of ionizable groups in low acidic conditions [8]. These prodrug-based nanomedicines retains their stability during the systemic circulation under normal physiological pH conditions (pH 7.4) while releasing the anti-tumor drugs in the tumor tissues (pH 6.5−7.0).

For instance, Zhang et al. combined doxorubicin (DOX) with the polymer backbone through acid-labile hydrazone bond to form polymeric DOX (PDOX) prodrug-based nanoparticles(Fig. 1a) [12]. Meanwhile, the photothermal agent of near-infrared (NIR)-absorbing dye IR825 and a targarting ligand of folic acid were modified to the self-assembled prodrug nanoparticles, respectively. Because of the acid-labile hydrazone linkage, the PDOX/IR825 could be readily triggered to release the conjugated DOX in the acidic TME(Fig. 1b**)**. Notably, significant tumor suppression performance was observed in the zebrafish liver hyperplasia model when they were treated with combined photothermal-chemotherapy of PDOX/IR825 nanomedicine **(**Fig. 1c). Furthermore, Hu et al. also developed a pH-responsive bortezomib (BTZ) dendrimer prodrug-based nanomedicine, which displayed prominent pH-dependent prototype drugs release behavior and good tumor inhibition [32].

3.1.2. GSH-responsive

The intracellular cytoplasm of cells contains more reductive species than the extracellular matrix. The concentration of GSH in the intracellular cytoplasm is two to three orders of magnitude higher than that in the extracellular matrixes [33]. Furthermore, GSH has a remarkable influence on many cell functions, including cell cycle regulation, gene expression, immune responses, protein function, and activation of cell death [34]. Meanwhile, there is evidence that the GSH level in tumor tissues is much higher than those in normal tissues [35]. During the past decades, the chemical bonds including disulfide bond, diselenide bond and some functional groups of *cis*,*cis*, trans-diamminedichlorodisuccinato-platinum (DSP) or trimethyl-locked benzoquinone (TMBQ) have been utilized to bridge anticancer drugs and polymers to synthesize GSH-responsive prodrug-based nanomedicines [8].

For example, Zhang et al. designed an engineered polymeric nanomedicine that loaded 59% of the GSH−responsive heterodimeric multifunctional prodrugs (HDMP) [36]. The CPT conjugated with a photosensitizer of 2−(1−hexyloxyethyl)−2−devinyl pyropheophorbide−α (HPPH) through a GSH−sensitive disulfide bond to form the HDMP. The obtained HDMP then co-assembly with degradable and biocompatible poly(ethylene glycol)−*block*−poly(d, l−lactic acid) (PEG−*b*−PLA) to compose HDMP−loaded NPs **(**Fig. 1d). The in vitro drugs release result demonstrated the CPT concentration released from CPT−ss−HPPH NPs increased over time **(**Fig. 1e). The in vivo results suggested that the HDMP NPs exhibited significant synergistic therapeutic efficiency **(**Fig. 1f**)**. In addition, Ling et al. fabricated the glutathione (GSH) sensitive self-assembled prodrug-based nanoparticles (NPs) that are composed of amphiphilic lipid-polyethylene glycol (PEG) and Pt(IV) prodrugs [11]. These prodrug NPs also exhibited significant glutathione responsiveness and good tumor inhibition rate.

3.1.3. ROS-responsive

Reactive oxygen species (ROS, e.g., hydroxyl radicals, H_2O_2, and superoxide), are a class of oxidative molecules produced in cells and involved in many biological processes. An appropriate concentration of ROS act as signaling molecules in many metabolic pathways, while excessive ROS are harmful to tissues and result in a series of diseases such as cancer. To be more specific, ROS act as signaling molecules that play crucial roles in protein translation, transcription, survival, tumorigenesis, and proliferation [37]. It is generally known that

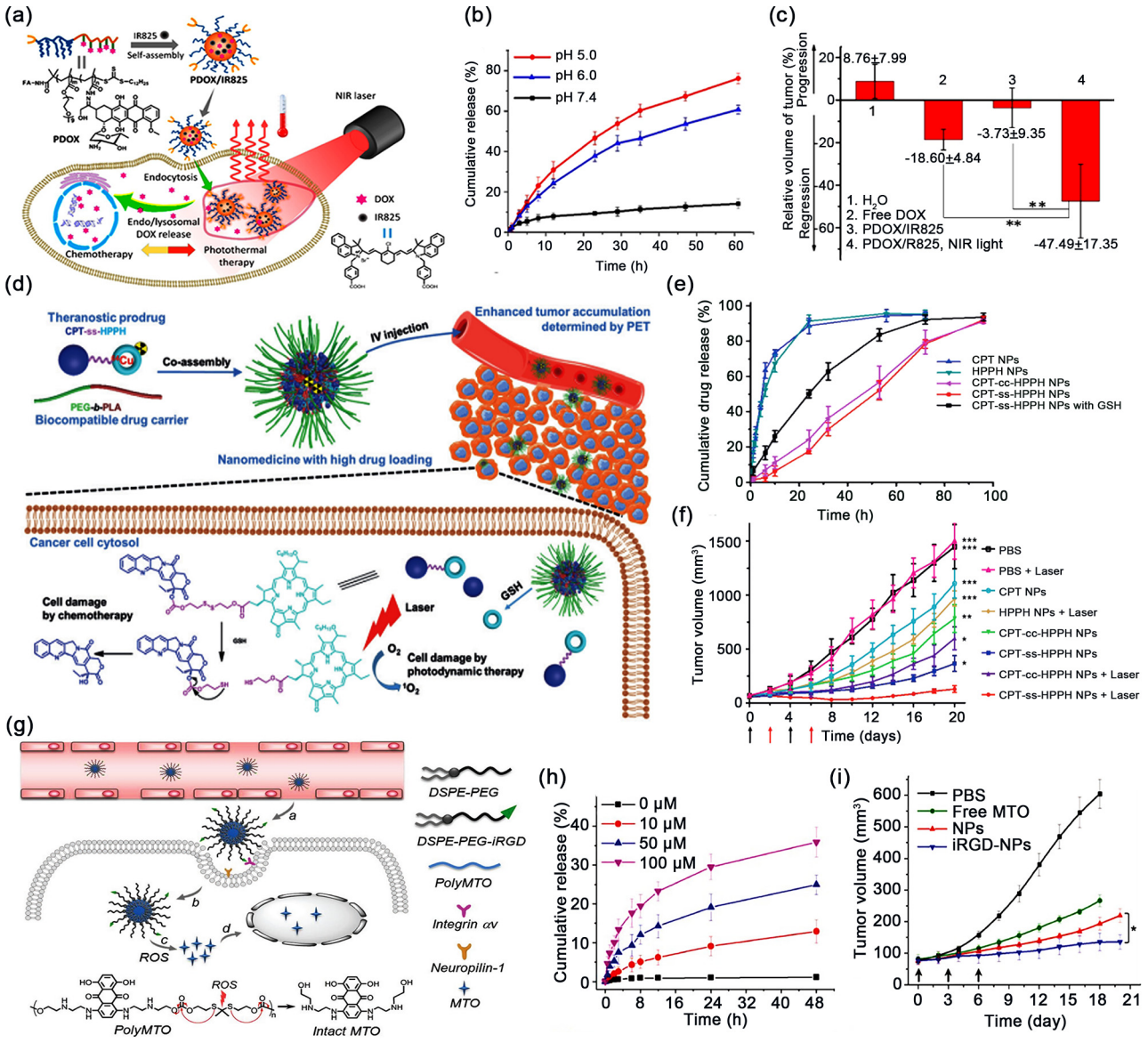


Fig. 1. (a) Schematic illustration of IR825 loaded PDOX prodrug NPs for targeted and combined PTT and chemotherapy. (b) In vitro DOX release from PDOX prodrug NPs in different pH at 37 C. (c) The relative tumor volume changes of transgenic zebrafish based liver tumor after different treatment. Reproduced with permission[12]. Copyright 2016, American Chemical Society. (d) Schematic illustration of GSH-sensitive HDMP (CPT-ss-HPPH) with high loading capacity for efficient drug accumulation in tumor and synergistic chemotherapy and PDT. (e) In vitro CPT release with or without GSH in PBS at 37 °C. (f) The tumor growth curves of tumor-bearing mice with different treatment ($n = 5$). Black arrows represent intravenous injection of drugs; red arrows represent laser irradiation. Reproduced with permission[36]. Copyright 2018, Wiley-VCH. (g) Schematic illustration of the polyMTO NP platform for targeted and deeply penetrating cancer therapy. (h) KO_2 concentrations-dependent release of MTO from the polyMTO NPs in PBS. (i) Tumor growth curve of the LNCaP xenograft tumor-bearing mice after various treatments. Reproduced with permission[10]. Copyright 2017, Wiley-VCH.

cancer cells in tumor tissues are immersed in intrinsic oxidative stress with a relatively higher level of H_2O_2 compared with healthy tissues, which plays a vital role in tumor cells proliferation and tumor progression [37]. Meanwhile, the oxidative stress inherent in the tumor tissue also promotes the increase of reactive oxygen species in the tumor. Due to the high ROS level in TME, many types of ROS-responsive nanomedicines have been developed.

For instance, Xu et al. developed a new ROS-triggered nanomedicine through copolymerizing clinical anticancer drug mitoxantrone (MTO, a NIR fluorescence drug) with a ROS-susceptible thioketal-containing linker (Fig. 1g) [10]. The prepared polyprodrugs were then self-assembled with lipid-PEG to form polyprodrug NPs. Internalizing RGD (iRGD) peptide was then employed to modify the polyprodrug NPs for targeting αv integrins on tumor endothelium. The in vitro results demonstrated that there was a dramatically improved and sustained drug release in the presence of ROS (Fig. 1h). The in vivo experiment suggested the prominent therapeutic efficacy of polyMTO NPs, and the iRGD modified NPs had better curative effects than other groups (Fig. 1i). Additionally, Li et al. utilized copolymerized monomers CPT and PEG as well as piperidine-modified methacrylate (P(CPTMA-co-PEMA)) to load glucose oxidase (GOD) to construct a prodrug-based polymersome nanoreactor (Fig. 2a). The obtained nanoreactor displayed H_2O_2-responsive CPT release behavior and superior tumor inhibition efficiency [20].

3.1.4. Enzyme-responsive

Enzymes are crucial targets for drug development due to their vital roles in cell regulation. The drugs can be delivered to the lesion site programmatically through enzyme-activatable carrier when the target site with higher concentrations of enzymes or the enzymatic activity is related to a specific tissue [38]. Owing to the importance of enzymes in tumor metabolism, tumor-associated enzyme

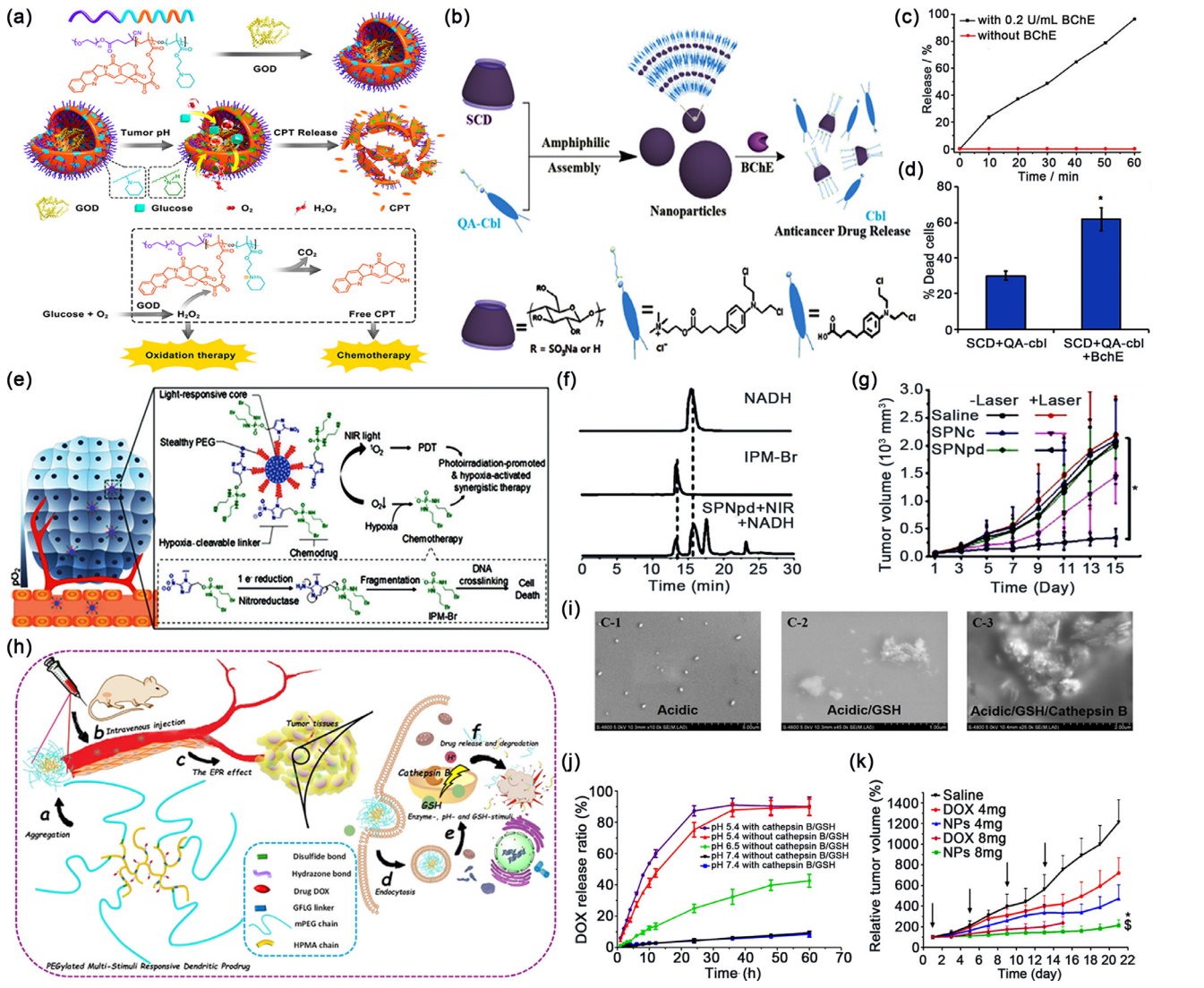


Fig. 2. (a) Schematic for the self-assembly process of GOD@PCPT-NR and its oxidation/chemotherapy for anticancer through tumor acidity-responsive activation, in situ H_2O_2 production, and active CPT drug release. Reproduced with permission[20]. Copyright 2017, American Chemical Society. (b) Schematic illustration of the cholinesterase-responsive SCD/QA-Cbl drug delivery system. (d) Percentage of Cbl released from the SCD/QA-Cbl assembly over time, with/without BChE. (e) Percentage of A549 tumor cells death in SCD/QA-Cbl assembly, with/without BChE. Reproduced with permission[13]. Copyright 2019, Royal Society of Chemistry. (e) Schematic of molecular mechanism of SPNpd for hypoxia-activated synergistic PDT and chemotherapy. (f) HPLC profiles of NADH, IPM-Br and the final solution of SPNpd incubated with NADH under hyoxia condition for 6 h. (g) Tumor volume changes of mice with different treatment. Reproduced with permission[42]. Copyright 2019, Wiley-VCH. (h) Schematic diagram for the structure of PEGylated multistimuli-responsive dendritic prodrug nanomedicine and its enhanced antitumor activity. (i) SEM images of the PEGylated dendritic polymeric prodrug nanomedicine after stored in acidic solution (C-1), acidic solution with GSH (C-2), and acidic solution with GSH/cathepsin B (C-3), respectively, for 24 h. (j) In vitro DOX release from the PEGylated multistimuli-responsive dendritic copolymer−DOX-based nanomedicine activated in different conditions. (k) Relative tumor volume of tumor-bearing mice after different treatments. Reproduced with permission[21]. Copyright 2018, American Chemical Society.

dysregulations have recently aroused attention in therapeutics. Using enzymes as a trigger has many favorable features in designing nanomedicine that can lead to numerous biochemical reactions under mild conditions nanomedicine [38]. Also, the exclusive selectivity of enzymes, allows sophisticated, specific, and biologically inspired reactions to occur [39]. Hence, many enzyme-cleavable chemical bonds were introduced into nanomedicines as targeted responses, especially for prodrug-based nanomedicines.

For example, Li et al. designed a smart Janus PEGylated dendrimer-PTX prodrug-based NPs, which was composed of PTX conjugated PEGlated peptide dendrimer and an enzyme cleavable linker oligopeptide glycyl phenylalanyl acylglycine showed a quickly release of PTX and significant tumor therapeutic effect in presence of enzyme [40]. Besides, Guan et al. reported a smart enzyme-responsive supramolecular nanoplatform, composed of biocompatible sulfato-b-cyclodextrin (SCD) and a water-soluble prodrug of choline modified anticancer drug chlorambucil (QA-Cbl) *via* electrostatic interactions (Fig. 2b) [13]. In this system, the butyrylcholinesterase (BChE) can cleave QA-Cbl into anti-cancer drug chlorambucil (Cbl) and choline due to the presence of a cleavable ester bond of QA-Cbl prodrug (Fig. 2c), resulting in well therapy performance against cancer cells (Fig. 2d).

3.1.5. *Hypoxia-responsive*

Owing to malformed tumor blood vessel progression and irregular tumor cells proliferation, hypoxia has been observed to emerge in solid tumors. As one of the main features of solid tumors, hypoxia is closely related to tumor metastasis, invasion, and drug resistance. Considering its critical roles in tumor angiogenesis, tumor progression, and cancer metastasis, hypoxia has been identified as a primary stimulus for cancer diagnosis and treatment [8], especially for prodrug-based nanomedicines. In addition, there are mainly three

representative classes of hypoxia-responsive moieties, including nitrobenzoyl alcohols, nitroimidazoles, and azo linkers. In general, these hypoxia-responsive moieties can accept electrons in hypoxic conditions, which would generate hydrophilic functional groups and further alter their physicochemical properties such as particle size and hydrophilicity [41].

Recently, Cui et al. constructed a semiconducting polymer nanoprodrug (SPNpd) for hypoxia triggered synergistic oncotherapy [42]. The photosentisizer SPN core was grafted with PEG to form an amphiphilic polymer brush and then conjugated with the chemodrug side chains (bromoisophosphoramide mustard intermediate, IPM-Br) *via* hypoxia-cleavable linkers and further self-assembly to form SPNpd (**Fig. 2e**). The obtained SPNpd possessed the features of generating singlet oxygen ($^1O_2$) under NIR irradiation that specifically tumor hypoxia-activatable drug release (**Fig. 2f**). Because of these characteristics, SPNpd could exert synergistic chemotherapy and PDT, and effectively inhibits tumor growth even in the hypoxic conditions (**Fig. 2g**). Also, Hua et al. designed a novel hypoxia-responsive angiopep-2-lipid-poly(MIs)n (ALP-(MIs)n) polyprodrug NP with hypoxic radiosensitization effects for targeted glioma therapy [43]. The ALP-(MIs)n polyprodrug NP comprised of P-(MIs)n (n = 25, 48), DSPE-PEG2000, angiopep-2-DSPE-PEG2000, and lecithin was prepared *via* nanoprecipitation process. The DOX was co-loaded into ALP-(MIs)n polyprodrug NP to achieve chemotherapy and radiation synergistic therapy. The obtained ALP-(MIs)n/DOX was disassembled and disordered to release DOX in the hypoxic conditions, and showed significant inhibition of glioma tumor growth with the assitance of RT.

3.1.6. Multi-stimuli-responsive

Given the complexity of TME, a combination of two or multiple stimuli in one nanoplatform can provide additional opportunities to maximize the therapy efficiency. Various endogenous stimuli, including low pH, GSH, ROS, enzymes, and hypoxia, coexist in the TME, as mentioned above, which opens up the possibility of designing a complex prodrug-based nanomedicine. Meanwhile, given the variations in the physiological TME, the multi-stimuli responsive nanomedicines can fully exploit the characteristics of the TME to enhance therapeutic accuracy. Thus, some multi-stimuli responsive prodrug-based nanomedicines have been developed in recent years

For example, Duan et al. developed a prodrug-based nanomedicine of PEGylated multistimuli-responsive dendritic copolymer coupled with DOX [21]. The dendritic polymers mainly consisted of poly [N-2-hydroxypropyl] methacrylamide (polyHPMA) segments and enzyme-responsive linkers of GFLG (Gly-Phe-Leu-Gly-tetrapeptide). Then the PEGylated (*via* the disulfide bond) dendritic polymers were further linked to DOX through hydrazine bonds (**Fig. 2h**). The proposed dendritic nanomedicines could respond to pH, GSH, and enzyme due to the characteristics of the bonds in the particles. For instance, the GFLG crosslinkers for enzymes-responsiveness, disulfide bonds for GSH-responsiveness, and hydrazine bones for acidity-responsiveness (**Fig. 2i and j**). Meanwhile, the dendritic polymers nanomedicines showed superior anti-tumor activity and tumor accumulation performance (**Fig. 2k**). Sun et al. reported ROS and GSH sensitive paclitaxel (PTX) prodrug-based nanoassemblies [44]. PTX was conjugated to citronellol (CIT) *via* disulfide bonds (SS) and further PEGylated. The obtained nanoassemblies showed redox-responsive drug-release behaviours and tumor remarkable growth inhibition performance.

3.2. Exogenous stimuli

3.2.1. Light-responsive

Because of non-invasiveness, inexpensiveness, and practicability, light has aroused tremendous interest as an exogenous stimulus for prodrug-based nanomedicines. The external photoactivatable prodrug-based nanomedicines have many advantages over other internal stimuli owing to ease of handling, precise control of the time and location of treatment [45]. Various light-responsive smart prodrug-based nanosystems utilizing ultraviolet (UV), visible light, and near-infrared (NIR) have been intensively applied for non-invasive and controlled on-demand drug release against cancer [46–48].

Since UV light (300–380 nm) can cause phase transitions in some polymers with special structures (such as O-nitrobenzyl, pyrene, spiropyran, and azobenzene), it is widely used in prodrug release [48,49–51]. For instance, Liu's group used a photocaged linkage to form prodrugs-based shell cross-linked (SCL) which were composed of P(CL-g-CPT)-b-P(OEGMA-co-MAEBA)-CPT and PCL-b-P(OEGMA-co-MAEBA-co-FA) amphiphilic diblock copolymers (**Fig. 3a**) [52]. This type of amphiphilic diblock copolymers micelles possessed a hydrophobic core conjugated with photocaged CPT prodrug. The cores of SCL micelles contained a lot of CPT drugs, which can be effectively cleaved to release drugs under UV irradiations (**Fig. 3b**). The in vitro results also revealed that SCL micelles exhibited at least ~9.7-fold enhanced cytotoxicity when introducing the UV light (**Fig. 3c**). Although many UV-responsive prodrug-based platforms have been developed, the limited permeability and potential hazards of UV light terribly inhibited the potential clinic translations.

Compared to UV light, visible light has a longer wavelength, which makes it more permeable to tissues and safer to clinical applications. Therefore, visible light is often used as a stimulant to programmatically regulate drug release. Zhou et al. conjugated the trans- $[Pt(N_3)_2(OH)_2(py)_2]$ complex with PEG and polyurethane to form a prodrug-backboned block copolymer (BCP) micelles (**Fig. 3d**) [53]. The light with a wide range of wavelengths (from 365 to 500 nm) can activate the BCP micelles to release drugs. Meanwhile, BCPs were inactivated and kept in the silenced Pt(IV) prodrug state without light irradiation (**Fig. 3e**). When irradiated with light, the chain was cleaved, then BCP micelles disassociated, and the Pt(IV) prodrugs were activated. Furthermore, the BCP micelles with good biocompatibility displayed significant antitumor activity (**Fig. 3f**).

The limitations of UV or visible light-triggered prodrug-based nanomedicines mainly contains low penetration depth (~10 mm), which prevents them from activating nanomedicines inside the tumor, resulting in poor therapeutic efficacy, therefore an urgent need to introduce NIR (700–1000 nm) light [54,55]. For instance, upconversion nanoparticles (UCNPs) were ideal nanoplatforms for NIR-responsive drug delivery. Yuan et al. combined the polyelectrolyte (CPE)–drug conjugate and UCNPs to form NIR-responsive prodrug-based nanomedicines (**Fig. 3g**) [56]. The main component of this nanomedicine was DOX conjugated PEGylated CPE photosensitizer, and a UV-cleavable ortho-nitrobenzyl (NB) linker as well as UCNPs. In the presence of a 980 nm laser, the UCNPs emitted UV and visible light to activate the polymer photosensitizer to generate ROS and release DOX for suppression of U87-MG cell growth.

3.2.2. Thermo responsive

In addition to the above stimuli, heat can act as an exogenous stimulus for controlled drugs release *via* thermo-sensitive polymer-based nanoparticles, liposomes or polymer micelles [57]. Thermo-sensitive nanocarriers are formulated based on heat-responsive polymers with drug conjugation and release drugs at a critical temperature point [58]. Commonly, thermo-sensitive polymeric prodrugs undergo a change in solubility behavior at the transition temperature, mainly include the lower and upper critical solution temperature (LCST and UCST), which are the temperature for more and less soluble transition states, respectively. In the light of this, a variety of thermoresponsive prodrugs systems has been devised, including liposomes, polymeric micelles, or nanogels [59,60].

Lv et al. reported a nanoplatform consisting of marimastat (MATT)-loaded thermosensitive liposomes (LTSLs) (MATT-LTSLs) and hyaluronic acid (HA)-paclitaxel (PTX) (HA-PTX) prodrugs (**Fig. 3h**) [31]. At 42 °C, near the phase transition temperature of LTSLs, HA-

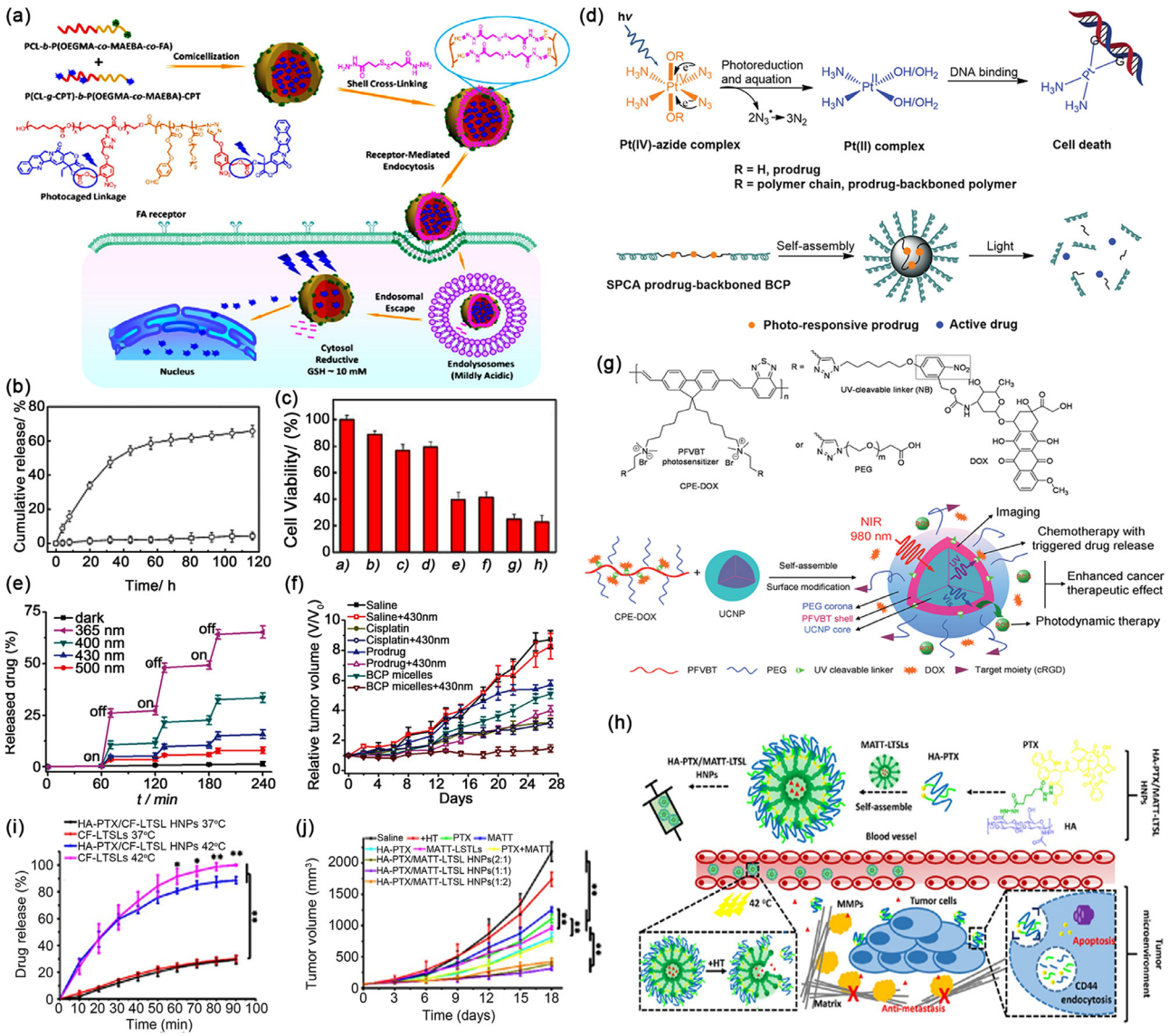


Fig. 3. (a) Schematic illustration of the fabrication of SCL micelles from P(CL-g-CPT)-b-P(OEGMA-co-MAEBA)-CPT and PCL-b-P(OEGMA-co-MAEBA-co-FA) amphiphilic diblock copolymers. (b) In vitro CPT release curves of SCL micelles (◯) with and (□) without UV irradiation; (c) Cell viability of HepG2 cells and (e) A549 cells administered with a) control, b) UV irradiation, c) FA-decorated SCL micelles, d) FA-free SCL micelles, e) FA-decorated SCL micelles + UV irradiation, f) FA-free SCL micelles + UV irradiation, g) CPT parent drug, and h) CPT parent drug + UV irradiation. Reproduced with permission[52]. Copyright 2013, American Chemical Society. (d) Schematic diagram of antitumor mechanism of photo-responsive Pt(IV)−azide complexes, and self-assembly as well as light-triggered dissociation of an SPCA prodrug-backboned BCP micelle. (e) Platinum release curves of BCP micelles with intermittent light irradiation. (f) Tumor growth inhibition curves of A549 bearing nude mice after different treatments. Reproduced with permission[53]. Copyright 2016, Wiley-VCH. (g) Chemical structure of the PEGylated CPE covalently linked with anticancer drug DOX via a UV-cleavable linker CPE−DOX and schematic diagram of NIR laser regulated initiation of the photosensitizer for photodynamic therapy and on-demand drug release for chemotherapy. Reproduced with permission[56]. Copyright 2014, Royal Society of Chemistry. (h) Schematic diagram of HNP preparation and possible mechanism for metastatic breast cancer therapy. (i) In vitro release curve at 42 or 37 °C. (j) Tumor volume changes of 4T1 tumor-bearing mice. Reproduced with permission[31]. Copyright 2018, American Chemical Society.

PTX/MATT-LTSLs HNPs released their payloads at a dramatically faster rate than that at 37 °C (Fig. 3i). Tumor growth, metastasis, and angiogenesis (10-fold) were significantly inhibited after the injection of HNPs with mild hyperthermia addition (Fig. 3j). The thermosensitive gel is also an attractive carrier to deliver prodrugs. For example, Peng et al. synthesized thermal and redox dual responsive biodegradable prodrug nanogels, which were composed of N-vinylcaprolactam (VCL) and N-succinimidyl methacrylate (Suma) crosslinked with diallyl disulfide (Fig. 4a) [61]. Good thermally controlled drug release behavior and significant antitumor performance toward HeLa cells were observed for this nanogel.

3.2.3. Ultrasound-responsive

Sonication is considered as a non-invasive, generally available, relatively inexpensive and portable technique that can penetrate deeply and accurately into the tissues. Recently, it has been used extensively in the biomedical field, such as imaging-guided drugs and gene delivery. Ultrasound (US) can trigger the release of the drugs through the thermal and mechanical generated from cavitation phenomena [62]. For example, Gao et al. developed an ultrasound activated prodrug delivery nanodroplet of PFP/C9F17-PAsp(DET)/CAD/PGA-g-mPEG, which was composed of acid-cleavable DOX prodrug, cationic amphiphilic fluorinated polymer carrier, and US responsive phase-change contrast agent aiming to achieve optimized US imaging, cellular uptake and antitumor therapeutic effect (Fig. 4b) [63]. Furthermore, Luo et al. developed an US-triggered and pH-sensitive DOX prodrug-microbubble complex (DPMC) (Fig. 4c) [64]. The DOX prodrug (DP) was composed of succinylated-heparin conjugated with DOX through hydrazone linker and modified with dual targeting ligands cRGD peptide and folate, and further combined with

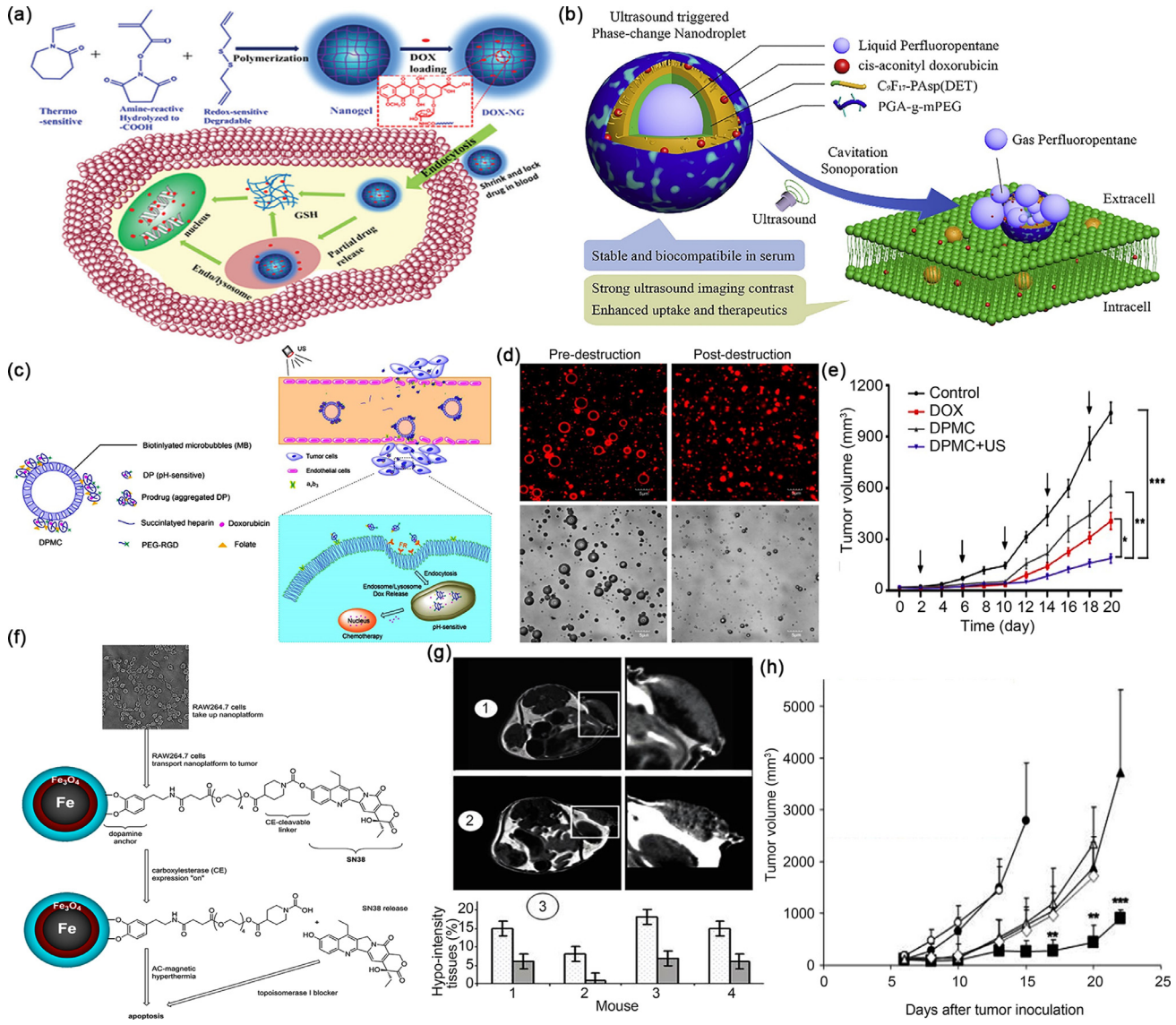


Fig. 4. (a) Scheme of synthesis of prodrug nanogel and intracellular release mechanism of DOX. Reproduced with permission[61]. Copyright 2018, American Chemical Society. (b) Construction of PFP-TNDs and the mechanisms of US-triggered imaging as well as delivery of cis-aconityl doxorubicin (CAD). Reproduced with permission[63]. Copyright 2019, Elsevier. (c) Schematic diagram of US combined with DPMC to deliver DOX into cell nuclei and induce cytotoxicity. (d) CLSM images and bright field images of DPMC pre-destruction and post-destruction by US. (i) In vivo tumor growth suppression of DPMC with/without US. Reproduced with permission[64]. Copyright 2017, Lvyspring. (f) Schematic illustration of RAW264.7 cell delivered thermochemotherapy. Reproduced with permission[67]. Copyright 2012, Beilstein. (g) T2-weighted images of the tumors obtained at 2 h-postinjection of USPIO/SQgemNPs ① without an external magnetic field (MF) (mouse 2) and ② with an external MF (1.1 T) (mouse 3). ③ Percentage of the hypo-intensity tissues with T2 < 36 ms (white column), and with T2 < 20 ms (gray column). Mouse 2 was injected with nanocomposites without exposure to MF. Mice 1, 3, and 4 were injected with USPIO/SQgem NPs with exposure to 1.1 T MF for 2 h. (g) In vivo anticancer activity of USPIO/SQgem NPs (with 1.1 T MF) compared with placebo-treated group (drug unloaded USPIO/squalene nanocomposites), USPIO/SQgem NPs (without MF), with SQgem NPs, and with free gemcitabine in L1210 tumor bearing mice. Untreated (•), placebo USPIO/squalene NPs (○), gemcitabine (◊), SQgem NPs (▲), USPIO/SQgem composite NPs (no MF) (Δ), USPIO/SQgem composite NPs (with 1.1 T MF) (□). Reproduced with permission[18]. Copyright 2011, American Chemical Society.

microbubble (MB) through an avidin-biotin bridge. The obtained DPMC possessed enhanced therapeutic efficiency with the assistant of US cavitation and sonoporation. Notably, after US treatment, DPMC was destroyed, and the aggregated DP dispersed into small uniform nanoparticles, thereby releasing DOX (Fig. 4d). In particular, the antitumor ability of DPMC with US irradiation in vivo was dramatically promoted (Fig. 4e).

3.2.4. *Magnetism and electric field - responsive*

Magnetic responsive prodrugs are either fabricated by entrapment of inorganic magnetic nanocrystals within polymeric scaffold or by covalent immobilization [65]. So far, two different strategies are using for polymer contraction/shrinkage: alternating magnetic (AMF) field on magnetic nanoparticles (MNPs) to generate thermal to release prodrugs and introducing the static magnetic field to generate mechanical force to release the prodrugs [66]. For example, Wang et al. developed a magnetic heat responsive nanoplatform that was composed of a core/shell Fe/Fe_3O_4 MNPs and the prodrugs of SN38 (a topoisomerase I blocker) (Fig. 4f) [67], showing accelerated SN38 release under action of the Tet-On Advanced system.

Additionally, utilizing a magnetic field for local area targeting would dramatically enhance the drug accumulation in tumors, and promoted the diagnosis (magnetic guided imaging) accuracy [68]. Hence, magnetically responsive systems provide a precise selection of prodrug delivery. Above all, the magnetic-guided targeting concept has proven great potential in cancer therapy. Recently, Arias et al. designed a novel theranostic nanomedicine with the ability to target the delivery of the gemcitabine prodrug under the assistant of the

magnetic field, monitored by the MRI imaging method as well (Fig. 4g) [18]. This multifunctional nanomedicine was prepared by embedding magnetite nanoparticles into a lipophilic self-assembling bioconjugate of squalenoyl gemcitabine (SQgem). The obtained nanomedicine had high drug loading efficiency about 93%, prominent magnetic susceptibility, and low burst release. Furthermore, magnetite/SQgem nanocomposites with magnetic field assistance showed considerably greater antitumor ability than the other groups (Fig. 4h).

Furthermore, the electric field is another emerging method to trigger the release of prodrugs. For example, J. Norman et al. presented a new concept of electroceuticals, summarized as the electrochemical activation of metal-based prodrugs [69]. However, due to the limitations of the electric field applied in vivo, there is little research on this part. It is believed that with the development of electrochemical activation prodrugs, the research on electric field-activated prodrugs-based nanomedicines will gradually emerge.

4. Applications in clinical translation

The history of the prodrugs-based nanomedicines composed of drugs and polymers is ancient and promotes the development of advanced stimuli-responsive drug release systems [70,71]. So far, some polymeric prodrugs have been approved as promising therapeutic nanoagents that already entered in clinical trial phase I/II as given in Table 1 [72,73]. All these promising clinical prodrug-based nanomedicines are very easy to be fabricated. Contradictory, most of the developed intelligent prodrug-based nanomedicines were designed with sophisticated structures and formulations in order to obtain smart properties, which is challenging to scale up for industrial productions. Therefore, simplifying the structures of prodrug-based nanomedicines is still one of the critical points for successful clinic translation.

Besides, the numbers of optimizations and improvements are also needed before the clinic translation. Especially, endogenous triggers (such as pH, enzyme) are difficult to control because of considerable variation from one individual to another. While the exogenous stimuli-responsive systems are much easier to be controlled and more promising for the clinic translation, however, problems such as normal tissue damage and tissue-penetration depth should be solved [45]. Accordingly, more attention should be paid on precisely controlling the prodrug conjugation process, high batch-to-batch reproducibility, and industrial scale-up possibility. The standard production methods and stimuli dosage control may eventually speed up the translation of prodrugs-based nanomedicines from the bench to the clinic.

Although prodrugs-based nanomedicines face many challenges in clinical application, one special prodrug of antibody-drug conjugates (ADCs) is attracting more and more attention in clinical practice. As a next-generation precision prodrug, ADCs has been envisioned as a viable approach towards a cure to various types of cancers to be used in clinic [74]. ADCs can be defined as a prodrug that utilizes the site-specific quality of a monoclonal antibody (mAb) to deliver a highly potent cytotoxic drug (warhead) via a chemically engineered biodegradable linker [74]. ADCs drugs are similar to other common prodrugs with the natural advantage of avoiding damage to normal tissue; its cytotoxic agent remains inactive during circulation in the body and releases the drug only upon entering tumor cells. Generally speaking, the mAb of ADCs can specifically bind to the targeted antigens that are typically highly expressed on the surface of cancer cells to achieve cancer therapy. Due to high stability, selectivity, and favorable pharmacokinetic characteristics of ADCs nanomedicines, many of these are applied in the clinic. Some clinic data is also presented for the researcher: for example, a famous clinical ADCs approved in 2000, gemtuzumab ozogamicin, composed of an anti-CD33 mAb and calicheamicin [75]. This drug was aimed to be used on patients older than 60 years old diagnosed with relapsed acute myeloid leukemia, whose response rate was about 30%. Furthermore, the approved dosage of this drug is very low, which is about 9 mg/m^2 or 0.22 mg/kg for an adult (65 kg), reflecting the high efficacy of calicheamicin.

As another representative Food and Drug Administration (FDA) approved ADCs drug, trastuzumab emtansine (T-DM1); which was formed by conjugation of anti-HER2 mAb trastuzumab with maytansinoid DM1 via linker for metastatic breast cancer therapy [75]. A clinical trial demonstrated that about a 33% response rate was observed after 110 patients with third-line metastatic breast cancer received the treatment of T-DM1 with the dosed of 3.6 mg/kg every three weeks, confirming the activity of T-DM1 in treatment-resistant HER2 positive metastatic breast cancer.

In addition to these drugs, by 2019 five other ADCs drugs: brentuximab vedotin(response rate of 54%) [75], ado-trastuzumab emtansine (response rate of 43.6%) [76], inotuzumab ozogamicin (response rate of 57%) [77], polatuzumab vedotin-piiq (response rate of 89%) [78], enfortumab vedotin (response rate of 44%) [79], have been approved by the FDA and are currently widely applied to treat cancer patients. With the rapid development of ADCs, according to incomplete statistics, there are currently about six hundred types of ADCs in clinical trials, and over 80 ADCs expected to be approved over the next few years [80]. Predictably, ADCs will be the main force of prodrug in clinical application and will play an increasingly important role in treating cancer. Meanwhile, we firmly believe that nanomedicines based on ADCs prodrugs will also step onto the clinical stage one day.

5. Conclusion and perspectives: challenges and outlook

Despite the above-mentioned stimuli-responsive prodrugs-based nanomedicines are available for clinical applications. The potential toxicity, accumulation in the body, and biodegradability of the

Table 1
Current status of some polymeric prodrugs in cancer therapy.

Coupled drugs	Polymers	Clinical Trials	Company
Aspartic acid	PEG	I	NCI
CPT	PEG	II	Enzon
CPT	Poly (glutamate)	III	Cell Therapeutics
CPT	Poly N-(2-Hydroxypropyl) methacrylamide (P-HPMA)	I	Pharmacia
Cisplatin	PEG-b-p(Glu)	III	NanoCarrier/Orient EuroPharma
DOX	P-HPMA	II	Pharmacia
DOX micelle and Platinate	P-HPMA	II/III	Access Pharma
DOX-Galactosamine	P-HPMA	II	Pharmacia
Docetaxel	$mPEG_{5000}$-b-p(HPMAm-Lac_n)	I	Cristal Therapeutics
DACH-Platinum	PEG-b-p(Glu)	I	NanoCarrier
Epirubicin	PEG-b-p(Asp-hydrazone)	I	NanoCarrier
PTX	P-HPMA	I	Pharmacia
PTX	PEG	I	Pharmacia
PTX	PEG-*b*-p(ASP-4-phenyl-1- butanol)	III	NanoCarrier/Nippon Kayaku

nanomedicines should be considered. For instance, acrylic acid-derived polymers cannot degrade in the aqueous phase, thus leads to the possible neurotoxicity [81]. Furthermore, the insufficient excretion of macromolecular conjugates leads to the accumulation in the body and harms the kidney [82]. Though stimuli-responsive prodrugs-based nanomedicines exhibited the efficient drug release ability after internalization in tumor or responded to TME. However, the drug-conjugates are also susceptible to non-specific and slow drug release in non-cancerous cells [83,84].

So far, basic research has been well-explored for achieving the "clinical prospects," but still, many of them might never enter into the clinic practices. Various probable obstacles have been portrayed as: Firstly, nanocarriers should be smart enough to cross biological barriers. Unfortunately, numerous of the nanomedicines is injected intravenously into the body, which would face a series of complex biological barriers that significantly limit the site-specific targeting. Due to the presence of opsonization, the mononuclear phagocyte system (MPS), cellular internalization, enormous intratumoral pressure, escaping from endosomal and lysosomal sections, as well as drug efflux pumps are the main obstacles to cross the biological barriers [85–87]. Furthermore, administration routes, disease types, and progression are also substantial challenges while designing smart prodrug delivery systems. Secondly, pharmaceutical manufacturing procedures should be safe, effective, and quality controlled. Many questions need to be addressed, such as biosafety, biodegradability, and metabolites of the nanomaterials. Moreover, compared with conventional drug delivery systems, prodrug-based nanomedicine may be more susceptible to inter-subject variability, particularly in therapy performance, therefore raising concerns with reproducibility in efficiency and safety. Thirdly, batch-to-batch reproducibility, scale-up validation, and controllable physicochemical properties are critical concerns for clinical interpretations. Authentication of the procedures should be confirmed for the designing and practices of prodrugs nanocarriers. For instance, stability, specificity, precision, and repeatability. In short, entirely, these issues argue the clinical applications of stimulus-sensitive drug carriers. Finally, to have a sound effect for nanotechnology to be incorporated with the pharmaceutical industry, it is worthy of designing a clear regulatory agenda to support novel nanomedicine products.

Combining the polymers with an active functional group (hydroxyl, carboxyl or halogen) and drug molecules to form the polymeric prodrugs is the most common strategy for constructing prodrugs-based nanomedicines. Meanwhile, the polymer with the appropriate stimuli-responsive linker is a critical factor in the construction of the required prodrug. Although the field of polymeric prodrug design principles is well defined, it is still difficult to select the appropriate linker to meet the design requirements with keeping the activity of the drug. Among them, the major challenge is to understand the relationship between efficient conjugates design and biological features such as tumor heterogeneity, microenvironment, and metastasis. The progress brings in the designing of more efficient bio-conjugates for combination therapy using polymeric prodrugs with degradable long-circulating conjugates. Moreover, the implementation of new targeting strategies is also vital by using different bio-ligands in combination with other imaging techniques. The new targeting strategies with the more advantageous features may include (1) novel polymeric conjugates design for directly stem cells targeting; (2) modulation of polymeric conjugates to therapeutic vaccines; (3) subcellular targeted polymeric conjugates; (4) designing of polymeric conjugates as lysosomotropic nanomedicines; (5) antibodies-polymeric prodrugs conjugation for cancer therapy; (6) polymeric conjugates as anti-angiogenic agents; (7) development of biochemical, optical and chemical sensors based on polymeric conjugates; (8) design anticancer nanomedicine using polymeric conjugates; (9) genetically and hereditary disorders therapies *via* synthetic genetic polymeric conjugates. Finally, a strong belief is that prodrug-based nanomedicines incorporated with the interdisciplinary approach of sciences have great potential in the clinical treatment of cancer.

6. Outstanding questions

This review presents the current development and recent progress in stimuli-responsive prodrug-based nanomedicines. Understanding various stimuli-responsive pathways of prodrug-based nanomedicines could promote the design optimization of related drugs and advance their clinical application prospects. Several prodrug based nanomedicines have entered the clinical stage and achieved promising clinical results, but more future studies about pharmaceutical and pharmacokinetic, solubility, stability, biosafety, biocompatibility, and biodegradability of prodrug-based nanomedicines still need to be explored, which would further improve their feasibility, thereby obtaining the optimization of prodrug-based nanomedicines in clinical application. This timely review article provides deep insights into the development and challenge of stimuli-responsive prodrug-based nanomedicines for cancer therapy, which will help the researcher to understand the mechanism of prodrug-based nanomedicines effectively and establish a solid foundation for their clinical applications.

7. Search strategy and selection criteria

Research data of this review were searched by Google Scholar, PubMed, and Web of Science using the search terms nanomedicine, prodrug, stimuli-responsive, cilinic application, and ADCs to obtain relevant articles. Information was included when related directly to the relationship between nanomedicine, prodrugs and stimuli-responsive. Only articles published in English between 1995 and 2019 were included, and mostly articles are between 2015 and 2019.

Declaration of competing Interests

The authors declare no conflict of interest.

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Author's contributions

J.O., B.S., and W.T. conceived the review out from our recently published work. A.X., H.S., and O.J presented the outline of this review. A.X., H.S., O.J., and Z.T. collected literature as well as wrote the review. N.K., N.Y.K., B.Q., D.P., B.S. and W.T. revised the manuscript, provided some relevant insights, and made some edits. All authors read and approved the final version of the manuscript.

Reference

[1] Yang G, Xu L, Chao Y, et al. Hollow MnO_2 as a tumor-microenvironment-responsive biodegradable nano-platform for combination therapy favoring antitumor immune responses. Nat Commun 2017;8(1):902.
[2] Bai S, Gao Y-E, Ma X, et al. Reduction stimuli-responsive unimolecular polymeric prodrug based on amphiphilic dextran-framework for antitumor drug delivery. Carbohydr Polym 2018;182:235–44.
[3] Ouyang J, Wang L, Chen W, et al. Biomimetic nanothylakoids for efficient imaging-guided photodynamic therapy for cancer. Chem Commun 2018;54(28):3468–71.
[4] Ouyang J, Deng L, Chen W, et al. Two dimensional semiconductors for ultrasound-mediated cancer therapy: the case of black phosphorus nanosheets. Chem Commun 2018;54(23):2874–7.

[5] Zhang L, Wang Z, Zhang Y, et al. Erythrocyte membrane cloaked metal–organic framework nanoparticle as biomimetic nanoreactor for starvation-activated colon cancer therapy. ACS Nano 2018.
[6] Tao W, Ji X, Zhu X, et al. Two-dimensional antimonene-based photonic nanomedicine for cancer theranostics. Adv Mater 2018;30(38):1802061.
[7] Strozyk MS, Carregal-Romero S, Henriksen-Lacey M, Brust M, Liz-Marzán LM. Biocompatible, multiresponsive nanogel composites for codelivery of antiangiogenic and chemotherapeutic agents. Chem Mater 2017;29(5):2303–13.
[8] Lu Y, Aimetti AA, Langer R, Gu Z. Bioresponsive materials. Nat Rev Mater 2016;2:16075.
[9] Luo C, Sun J, Sun B, He Z. Prodrug-based nanoparticulate drug delivery strategies for can- cer therapy. Trends Pharmacol Sci 2014;35(11):556–66.
[10] Xu X, Saw PE, Tao W, et al. ROS-responsive polyprodrug nanoparticles for triggered drug delivery and effective cancer therapy. Adv Mater 2017;29(33):1700141.
[11] Ling X, Tu J, Wang J, et al. Glutathione-Responsive Prodrug Nanoparticles for Effective Drug Delivery and Cancer Therapy. ACS Nano 2019;13(1):357–70.
[12] Zhang Y, Teh C, Li M, et al. Acid-Responsive Polymeric Doxorubicin Prodrug Nanoparticles Encapsulating a Near-Infrared Dye for Combined Photothermal-Chemotherapy. Chem Mater 2016;28(19):7039–50.
[13] Guan X, Chen Y, Wu X, Li P, Liu Y. Enzyme-responsive sulfatocyclodextrin/prodrug supramolecular assembly for controlled release of anti-cancer drug chlorambucil. Chem Commun 2019;55(7):953–6.
[14] Cui D, Huang J, Zhen X, et al. A semiconducting polymer nano-prodrug for hypoxia-activated photodynamic cancer therapy. Angew Chem Int Ed 2019;58(18):5920–4.
[15] Sun B, Luo C, Yu H, et al. Disulfide bond-driven oxidation- and reduction-responsive prodrug nanoassemblies for cancer therapy. Nano Lett 2018;18(6):3643–50.
[16] Dai Y, Xiao H, Liu J, et al. In Vivo multimodality imaging and cancer therapy by near-infrared light-triggered trans-platinum pro-drug-conjugated upconverison nanoparticles. J Am Chem Soc 2013;135:18920.
[17] McDaniel JR, Bhattacharyya J, Vargo KB, et al. Self-assembly of thermally responsive nanoparticles of a genetically encoded peptide polymer by drug conjugation. Angew Chem Int Ed 2013;52(6):1683–7.
[18] Arias JL, Reddy LH, Othman M, et al. Squalene based nanocomposites: a new platform for the design of multifunctional pharmaceutical theragnostics. ACS Nano 2011;5(2):1513–21.
[19] Wang J, Zhang X, Cen Y, Lin X, Wu Q. Antitumor gemcitabine conjugated micelles from amphiphilic comb-like random copolymers. Colloids Surf B 2016;146:707–15.
[20] Li J, Li Y, Wang Y, et al. Polymer prodrug-based nanoreactors activated by tumor acidity for orchestrated oxidation/chemotherapy. Nano Lett 2017;17(11):6983–90.
[21] Duan Z, Cai H, Zhang H, et al. PEGylated multistimuli-responsive dendritic prodrug-based nanoscale system for enhanced anticancer activity. ACS Appl Mater Interfaces 2018;10(42):35770–83.
[22] Cheetham AG, Chakroun RW, Ma W, Cui H. Self-assembling prodrugs. Chem Soc Rev 2017;46(21):6638–63.
[23] Teng W, Jia F, Han H, et al. Polyamino acid-based gemcitabine nanocarriers for targeted intracellular drug delivery. Polym Chem 2017;8(16):2490–8.
[24] Bai Y, Liu CP, Song X, et al. Photo- and pH- dual-responsive β-cyclodextrin-based supramolecular prodrug complex self-assemblies for programmed drug delivery. Chem–Asian J 2018;13(24):3903–11.
[25] Wang Y, Du J, Wang Y, Jin Q, Ji J. Pillar[5]arene based supramolecular prodrug micelles with pH induced aggregate behavior for intracellular drug delivery. Chem Commun 2015;51(14):2999–3002.
[26] Peng M, Qin S, Jia H, et al. Self-delivery of a peptide-based prodrug for tumor-targeting therapy. Nano Res 2016;9(3):663–73.
[27] Caron J, Maksimenko A, Wack S, et al. Improving the antitumor activity of squalenoyl-paclitaxel conjugate nanoassemblies by manipulating the linker between paclitaxel and squalene. Adv Healthc Mater 2013;2(1):172–85.
[28] Yue Z, Wang H, Li Y, et al. Coordination-driven self-assembly of a Pt(IV) prodrug-conjugated supramolecular hexagon. Chem Commun 2018;54(7):731–4.
[29] Fang T, Ye Z, Wu J, Wang H. Reprogramming axial ligands facilitates the self-assembly of a platinum(IV) prodrug: overcoming drug resistance and safer in vivo delivery of cisplatin. Chem Commun 2018;54(66):9167–70.
[30] Yang B, Wang K, Zhang D, et al. Light-activatable dual-source ROS-responsive prodrug nanoplatform for synergistic chemo-photodynamic therapy. Biomater Sci 2018;6(11):2965–75.
[31] Lv Y, Xu C, Zhao X, et al. Nanoplatform assembled from a CD44-targeted prodrug and smart liposomes for dual targeting of tumor microenvironment and cancer Cells. ACS Nano 2018;12(2):1519–36.
[32] Hu X, Chai Z, Lu L, et al. Bortezomib dendrimer prodrug–based nanoparticle system. Adv Funct Mater 2019;29(14):1807941.
[33] Chen H, Liu D, Guo Z. Endogenous stimuli-responsive nanocarriers for drug delivery. Chem Lett 2016;45(3):242–9.
[34] Huang R, Wang B-B, Si-Tu X-M, et al. A lysosome-targeted fluorescent sensor for the detection of glutathione in cells with an extremely fast response. Chem Commun 2016;52(77):11579–82.
[35] Lee MH, Sessler JL, Kim JS. Disulfide-based multifunctional conjugates for targeted theranostic drug delivery. Acc Chem Res 2015;48(11):2935–46.
[36] Zhang F, Ni Q, Jacobson O, et al. Polymeric nanoparticles with a glutathione–sensitive heterodimeric multifunctional prodrug for in vivo drug monitoring and synergistic cancer therapy. Angew Chem Int Ed 2018;57(24):7066–70.
[37] Peng X, Gandhi V. ROS-activated anticancer prodrugs: a new strategy for tumor-specific damage. Ther Deliv 2012;3(7):823–33.
[38] Dela Rica R, Aili D, Stevens MM. Enzyme-responsive nanoparticles for drug release and diagnostics. Adv Drug Deliv Rev 2012;64(11):967–78.
[39] Hu Q, Katti PS, Gu Z. Enzyme-responsive nanomaterials for controlled drug delivery. Nanoscale 2014;6(21):12273–86.
[40] Li N, Cai H, Jiang L, et al. Enzyme-Sensitive and Amphiphilic PEGylated Dendrimer-Paclitaxel Prodrug-Based Nanoparticles for Enhanced Stability and Anticancer Efficacy. ACS Appl Mater Interfaces 2017;9(8):6865–77.
[41] Thambi T, Park JH, Lee DS. Hypoxia-responsive nanocarriers for cancer imaging and therapy: recent approaches and future perspectives. Chem Commun 2016.
[42] Cui D, Huang J, Zhen X, et al. A semiconducting polymer nano–prodrug for hypoxia–activated photodynamic cancer therapy. Angew Chem Int Ed 2019;58(18):5920–4.
[43] Hua L, Wang Z, Zhao L, et al. Hypoxia-responsive lipid-poly-(hypoxic radiosensitized polyprodrug) nanoparticles for glioma chemo-and radiotherapy. Theranostics 2018;8(18):5088.
[44] Sun B, Luo C, Yu H, et al. Disulfide bond-driven oxidation-and reduction-responsive prodrug nanoassemblies for cancer therapy. Nano Lett 2018;18(6):3643–50.
[45] Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nat Mater 2013;12(11):991–1003.
[46] Schroeder A, Goldberg MS, Kastrup C, et al. Remotely activated protein-producing nanoparticles. Nano Lett 2012;12(6):2685–9.
[47] Yang G, Liu J, Wu Y, Feng L, Liu Z. Near-infrared-light responsive nanoscale drug delivery systems for cancer treatment. Coord Chem Rev 2016;320:100–17.
[48] Jia S, Fong W-K, Graham B, Boyd BJ. Photoswitchable molecules in long-wavelength light-responsive drug delivery: from molecular design to applications. Chem Mater 2018;30(9):2873–87.
[49] Azagarsamy MA, Alge DL, Radhakrishnan SJ, Tibbitt MW, Anseth KS. Photocontrol-led nanoparticles for on-demand release of proteins. Biomacromolecules 2012;13(8):2219–24.
[50] Tong R, Cheng J. Drug-initiated, controlled ring-opening polymerization for the synthesis of polymer–drug conjugates. Macromolecules 2012;45(5):2225–32.
[51] Cosa G, Lukeman M, Scaiano J. How drug photodegradation studies led to the promise of new therapies and some fundamental carbanion reaction dynamics along the way. Acc Chem Res 2009;42(5):599–607.
[52] Hu X, Tian J, Liu T, Zhang G, Liu S. Photo-triggered release of caged camptothecin prodrugs from dually responsive shell cross-linked micelles. Macromolecules 2013;46(15):6243–56.
[53] Zhou D, Guo J, Kim GB, et al. Simultaneously Photo–Cleavable and Activatable Prodrug–Backboned Block Copolymer Micelles for Precise Anticancer Drug Delivery. Adv Healthc Mater 2016;5(19):2493–9.
[54] Lee MH, Kim E-J, Lee H, et al. Liposomal texaphyrin theranostics for metastatic liver cancer. J Am Chem Soc 2016;138(50):16380–7.
[55] Rwei AY, Wang W, Kohane DS. Photoresponsive nanoparticles for drug delivery. Nano Today 2015;10(4):451–67.
[56] Yuan Y, Min Y, Hu Q, Xing B, Liu B. NIR photoregulated chemo-and photodynamic cancer therapy based on conjugated polyelectrolyte–drug conjugate encapsulated upconversion nanoparticles. Nanoscale 2014;6(19):11259–72.
[57] Fleige E, Quadir MA, Haag R. Stimuli-responsive polymeric nanocarriers for the controlled transport of active compounds: concepts and applications. Adv Drug Deliv Rev 2012;64(9):866–84.
[58] Karimi M, Ghasemi A, Zangabad PS, et al. Smart micro/nanoparticles in stimulus-responsive drug/gene delivery systems. Chem Soc Rev 2016;45(5):1457–501.
[59] Deka SR, Quarta A, Di Corato R, et al. Magnetic nanobeads decorated by thermoresponsive PNIPAM shell as medical platforms for the efficient delivery of doxorubicin to tumour cells. Nanoscale 2011;3(2):619–29.
[60] Topp M, Dijkstra PJ, Talsma H, Feijen J. Thermosensitive micelle-forming block copolymers of poly (ethylene glycol) and poly (N-isopropylacrylamide). Macromolecules 1997;30(26):8518–20.
[61] Peng H, Huang X, Oppermann A, et al. A facile approach for thermal and reduction dual-responsive prodrug nanogels for intracellular doxorubicin delivery. J Mater Chem B 2016;4(47):7572–83.
[62] Chen W-T, Kang S-T, Lin J-L, et al. Targeted tumor theranostics using folate- conjugated and camptothecin-loaded acoustic nanodroplets in a mouse xenograft model. Biomaterials 2015;53:699–708.
[63] Gao J, Yu B, Li C, et al. Ultrasound triggered phase-change nanodroplets for doxorubic-in prodrug delivery and ultrasound diagnosis: an in vitro study. Colloids Surf B 2019;174:416–25.
[64] Luo W, Wen G, Yang L, et al. Dual-targeted and pH-sensitive doxorubicin prodrug-microbubble complex with ultrasound for tumor treatment. Theranostics 2017;7(2):452–65.
[65] Kainz QM, Reiser O. Polymer-and dendrimer-coated magnetic nanoparticles as versa-tile supports for catalysts, scavengers, and reagents. Acc Chem Res 2014;47(2):667–77.
[66] Ulbrich K, Hola K, Subr V, et al. Targeted drug delivery with polymers and magnetic nanoparticles: covalent and noncovalent approaches, release control, and clinical studies. Chem Rev 2016;116(9):5338–431.
[67] Wang H, Shrestha TB, Basel MT, et al. Magnetic-Fe/Fe_3O_4-nanoparticle-bound SN38 as carboxylesterase-cleavable prodrug for the delivery to tumors within monocytes/macrophages. Beilstein J Nanotech 2012;3:444–5.
[68] Yang H-W, Hua M-Y, Liu H-L, et al. Self-protecting core-shell magnetic nanoparticles for targeted, traceable, long half-life delivery of BCNU to gliomas. Biomaterials 2011;32(27):6523–32.
[69] Norman DJ, González-Fernández E, Clavadetscher J, et al. Electrodrugs: an electrochemical prodrug activation strategy. Chem Commun 2018;54(66):9242–5.
[70] Putnam D, Kopeček J. Polymer conjugates with anticancer activity. Biopolymers Ii: Springer 1995:55–123.

[71] Yang X, Ding Y, Ji T, et al. Improvement of the in vitro safety profile and cytoprotective efficacy of amifostine against chemotherapy by PEGylation strategy. Biochem Pharacol 2016;108:11–21.
[72] Duncan R, Gac-Breton S, Keane R, et al. Polymer–drug conjugates. PDEPT PELT: basic Princ Des Transf Lab Clin 2001;74(1–3):135–46 J Control Release.
[73] Khandare J, Minko T. Polymer–drug conjugates: progress in polymeric prodrugs. Prog Polym Sci 2006;31(4):359–97.
[74] Sievers EL, Senter PD. Antibody-drug conjugates in cancer therapy. Annu Rev Med 2013;64:15–29.
[75] Alley SC, Okeley NM, Senter PD. Antibody–drug conjugates: targeted drug delivery for cancer. Curr Opin Chem Biol 2010;14(4):529–37.
[76] Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. New Engl J Med 2012;367(19):1783–91.
[77] Kantarjian H, Thomas D, Jorgensen J, et al. Inotuzumab ozogamicin, an anti-CD22–calecheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. Lancet Neurol 2012;13(4):403–11.
[78] Deeks ED. Polatuzumab vedotin: first global approval. Drugs 2019;79(13):1467–75.
[79] Rosenberg JE, O'Donnell PH, Balar AV, et al. Pivotal trial of enfortumab vedotin in urothelial carcinoma after platinum and anti-programmed death 1/programmed death ligand 1 therapy. J Clin Oncol 2019;37(29):2592.
[80] Coats S, Williams M, Kebble B, et al. Antibody–drug conjugates: future directions in clinical and translational strategies to improve the therapeutic index. Clin Cancer Res 2019;25(18):5441–8.
[81] LoPachin RM. Acrylamide neurotoxicity: neurological, morhological and molecular endpoints in animal models. Chemistry and safety of acrylamide in food: Springer; 2005. p. 21–37.
[82] Han TH, Zhao B. Absorption, distribution, metabolism, and excretion considerations for the development of antibody-drug conjugates. Drug Metab Dispos 2014;42(11):1914–20.
[83] Cheng A-L, Kang Y-K, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Neurol 2009;10(1):25–34.
[84] Hou M, Gao Y-E, Shi X, et al. Methotrexate-based amphiphilic prodrug nanoaggregates for co-administration of multiple therapeutics and synergistic cancer therapy. Acta Biomater 2018;77:228–39.
[85] Lindner LH, Hossann M, Vogeser M, et al. Dual role of hexadecylphosphocholine (miltefosine) in thermosensitive liposomes: active ingredient and mediator of drug release. J Control Release 2008;125(2):112–20.
[86] Ji T, Lang J, Ning B, et al. Enhanced Natural Killer Cell Immunotherapy by Rationally Assembling Fc Fragments of Antibodies onto Tumor Membranes. Adv Mater 2019;31(6):1804395.
[87] Sharma A, Lee M-G, Shi H, et al. Overcoming drug resistance by targeting cancer bioenergetics with an activatable prodrug. Chem 2018;4(10):2370–83.