BIO Integration

Mini Review

The Integration of Reactive Oxygen Species Generation and Prodrug Activation for Cancer Therapy

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Abstract

The combination of chemotherapeutic drugs and reactive oxygen species (ROS) can improve cancer treatment outcome. Many ROS-generation strategies can specifically consume tumor-inherent oxygen and generate ROS, resulting in amplified ROS level and aggravated hypoxia. Therefore, the ROS generation strategy can integrate with prodrug activation strategy to realize synergetic therapy. In recent years, stimuli-responsive nanomedicines have been developed to realize the integration of ROS generation and prodrug activation. Triggered by a stimulus, nanomedicines can generate ROS at the tumor site, which can further activate the release of active drugs. In this review, we will summarize the latest progress of these nanomedicines and discuss the perspectives and challenges.

Keywords

Cancer therapy, hypoxia, nanomedicine, prodrug, reactive oxygen species.

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Introduction

Chemotherapy, a cancer treatment approach based on small-molecule chemotherapeutic drugs, has been widely used in the clinic [1–3]. By systemic administration of drugs, the proliferation of tumor cells can be inhibited. However, serious side effects may also be caused by chemotherapy because chemotherapeutic drugs can cause damage to both tumor cells and normal ones [4–7]. Prodrugs, which refer to a class of bioreversible drug derivatives, have attracted much attention [8]. Currently, approximately 10% of the marketed chemotherapeutic drugs worldwide are in the form of prodrugs [9]. Prodrugs do not show high pharmacological activity until they are activated; therefore, the development of prodrugs is an efficient strategy to improve the physicochemical, biopharmaceutical, or pharmacokinetic properties of drugs, overcoming drawbacks of parent drugs [10, 11].

In the past several decades, a variety of prodrugs that can be activated by in vivo stimuli such as pH, glutathione (GSH), and enzymes, have been developed (**Table 1**) [12–18], and some of which are already in clinical trial [19]. However, acidic condition and GSH are also presented in normal cells; therefore, the selectivity of commonly used pH- and GSH-responsive prodrugs is limited because these prodrugs can be partially activated by intracellular environments of normal cells. To improve the tumor selectivity of prodrug activation, various reactive oxygen species (ROS)–activated prodrugs based on ROS-sensitive bonds, such as thioketal bond and peroxalate ester, have been developed [20–26]. By exploiting nanotechnology, the ROS-responsive prodrugs and tumor-specific ROS-generating agents such as photosensitizers can be integrated into one nanomedicine. Through passive targeting, the nanomedicine will accumulate in tumor tissue. In response to certain stimulus, the nanomedicine will first generate ROS, which will further trigger the activation of ROS-responsive prodrugs, achieving chemo/ROS combination therapy. In addition, most of the ROS generation processes will consume inherent oxygen, resulting in exacerbation of tumor hypoxic environment [27–29]. Therefore, the integration of ROS-generating agents and hypoxia-activated prodrugs is also a promising approach to realize tumor-specific

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Table 1 Summary of Stimuli-Activatable Prodrugs in Cancer Therapy

Stimuli	Responsive Groups	Active Drugs	References
pH	Hydrazone bond	DOX	[62–65]
	Ketal linkage	Etoposide	[66]
GSH	Disulfide bond	CPT	[12–14, 18]
		DOX	[67]
		PTX	[68, 69]
	Diselenium bond	Docetaxel	[70]
ROS	Thioether bond	PTX	[41]
	Thioketal linker	DOX	[38, 39, 46]
		CPT	[25, 26, 37, 42, 50]
		PTX	[23]
		Cabazitaxel	[71]
		Mitoxantrone	[33]
		SS31	[72]
	Peroxalate ester linkage	CPT	[21, 49]
	Phenylboronic ester	DOX	[45]
		PTX	[73]
Enzyme	Ester bond	Mitoxantrone	[74]
		7-Ethyl-10-hydroxycamptothecin	[75, 76]
		DOX	[77]
Hypoxia	TPZ	TPZ radical	[56–60, 78, 79]
	AQ4N	AQ4	[32, 80, 81]
	Azobenzene linker	PTX	[54]
	Nitro groups	IPM-Br	[55]
Hydrogen sulfide	Sulfoxide linker	DOX	[82]
Thermo	Edman linker	DOX	[83]
	Azo bond	DOX	[84]

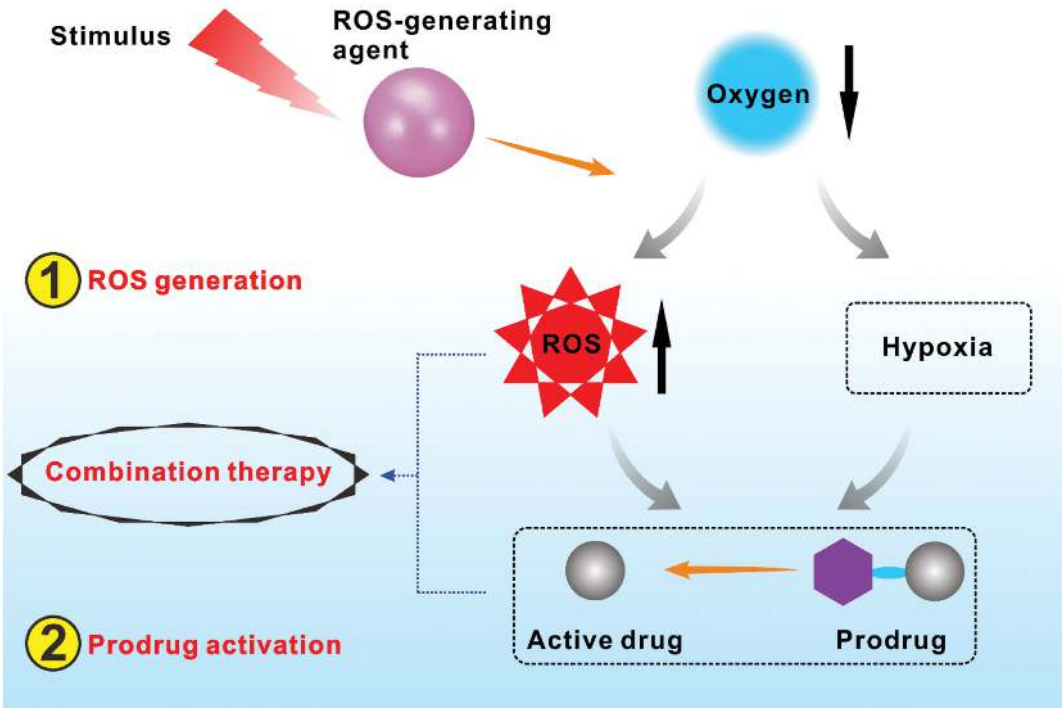

Figure 1 Schematic illustration of the integration of ROS generation and prodrug activation.

combination therapy (**Figure 1**). The hypoxia-responsive prodrugs consist based prodrug or polyprodrug; the other is the drug whose pharmacological activity can be activated in hypoxic environment, such as tirapazamine (TPZ) and 1,4-bis([2-(dimethylamino-*N*-oxide)ethyl] amino)5,8-dihydroxy- anthracene-9,10-dione) [30–32].

This review summarizes recent advances in the cancer therapeutic strategy combining ROS generation and prodrug activation. The representative nanomedicines and their applications in cancer therapy will be introduced. Finally, the perspectives and challenges of this therapeutic strategy will also be discussed.

ROS-triggered prodrug activation

By conjugating drug molecules with other small molecules or polymers through ROS-sensitive linkers, ROS-responsive prodrugs can be obtained [33]. In the presence of high levels of ROS, these prodrugs can be activated to release active drugs. Compared with normal tissue, cancer cells show higher level of ROS; however, the endogenous ROS is still insufficient to realize effective prodrug activation. In the past decades, various ROS generation approaches have been used to further increase the ROS level inside cancer and thus improve the responsivity of ROS-responsive prodrugs.

Among the ROS generation approaches, photodynamic therapy (PDT) is the most commonly used one [34–36]. Qian et al. reported a ROS-responsive nanomedicine self-assembled from amphiphilic prodrug for combined local-regional PDT and chemotherapy [37]. To prepare the amphiphilic prodrug, a photosensitizer pyropheophorbide-a (PPa) and a chemotherapeutic drug camptothecin (CPT) were conjugated to poly(ethylene glycol) (PEG) simultaneously (**Figure 2A**). In blood circulation, both CPT and PPa are inactive, resulting in reduced side effects to the healthy tissues. Upon laser irradiation, singlet oxygen will be first produced via PPa-mediated photodynamic process. Furthermore, the ROS will cleave the thioketal linker and thus lead to on-demand CPT release. Therefore, this nanomedicine can be used for combination of PDT and chemotherapy. Li et al. developed a ROS-activatable prodrug vesicle composed of unsaturated phospholipids, phospholipid-mimic doxorubicin (DOX) prodrug and PEG-modified PPa [38]. Under imaging-guided laser irradiation, ROS-mediated oxidation of unsaturated phospholipids and cleavage of thioketal linkers will lead to increased permeability of vesicle and DOX prodrug activation, allowing ultrafast DOX release. In another study, Wang's group developed a polyphosphoester-DOX conjugate-based polyprodrug nanoparticle (NP), in which the photosensitizer Ce6 was encapsulated [39]. This polyprodrug NP can achieve photo-triggered dissociation and prodrug activation. In a recent study, Wang et al. reported a ROS-responsive drug delivery nanosystem [26]. A thioketal linker-containing poly-CPT prodrug was modified to iron oxide nanoparticles (IONPs). Then the polyprodrug-modified IONPs and aggregation-induced emission (AIE) photosensitizer were encapsulated into a nanomicelle formed by pH-responsive amphiphilic polymer. Under white light irradiation, the singlet oxygen produced by AIE photosensitizer will cause CPT release. Moreover, due to the pH/ROS dual responsiveness, the nanomedicine can achieve two-stage size changes for enhanced drug delivery and fast elimination.

The design of ROS-responsive heterotypic drug-photosensitizer dimer represents another strategy to realize ROS-triggered prodrug activation [40]. Recently, Sun and colleagues reported a nanomedicine that which is based on a ROS-responsive dimer [41]. The dimer was prepared by conjugating paclitaxel (PTX) with PPa via a ROS-cleavable single thioether linker (**Figure 2B**). With the help of PEG-lipid, the dimer can self-assemble into PEGylated prodrug (PSP) NPs with ultrahigh loading capacity. Once the PSP NPs arrive on the tumor sites via the passive targeting effect, the endogenous ROS will lead to partial release of PPa and PTX through cleavage of thioether bond. The disassembly of PSP NPs will address the aggregation-caused quenching (ACQ) effect of PPa. Therefore, the ROS generation efficiency in light-triggered PDT process will be significantly improved. This self-facilitated ROS generation further triggered prodrug activation, resulting in dual-synergistic multimodal cancer therapy. In a recent study, Chen's group prepared a heterotypic dimer containing CPT and 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a (HPPH) [42]. The chemodrug and photosensitizer were linked by a cleavable thioketal linker. The dimer-loaded NPs showed high drug loading content without serious drug leakage. Under endogenous ROS and the ROS generated in PDT process, the HRC prodrug can be activated to achieve synergistic tumor inhibition.

Besides PDT, ROS can also be generated by chemical methods [43, 44]. For example, β-lapachone (Lap) can generate hydrogen peroxide through the catalysis of the

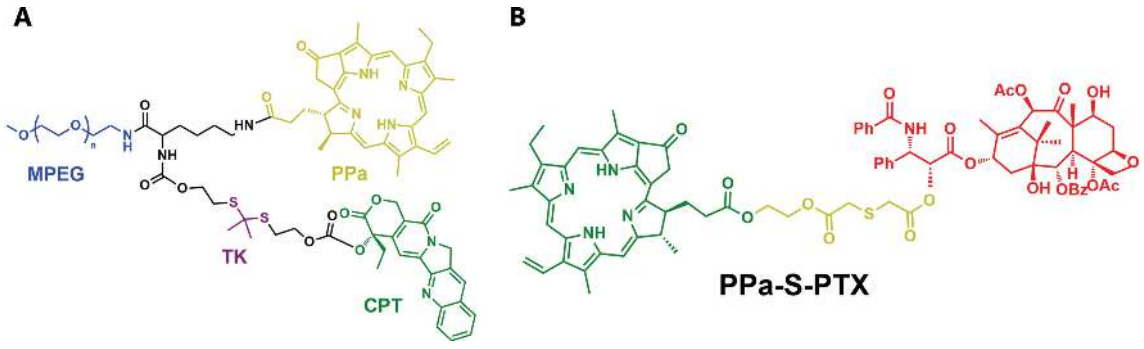

Figure 2 (A) Chemical structure of MPEG-(TK-CPT)-PPa. (B) Chemical structure of PPa-S-PTX dimer.

nicotinamide adenine dinucleotide (phosphate) (NAD(P)H): quinone oxidoreductase 1 (NQO1) enzyme. Due to NQO1 overexpression of tumor cells, Lap-based nanomedicine exhibits an extremely high selectivity. Rao and colleagues reported a nanomedicine by co-loading Lap and a ROS-responsive prodrug (BDOX) in a nanomicelle [45]. Once the nanomedicines enter NQO1-overexpressed cancer cells, they will first release Lap for improving the intracellular hydrogen peroxide level. Then the BDOX prodrug will be activated by hydrogen peroxide to release free DOX. More importantly, the sequential drug release process allows the synergy of Lap and DOX to prevent drug efflux, resulting in reversal of multidrug resistance of cancer cells. The cytotoxicities of nanomedicines against NQO1-overexpressing cancer cells (4T1, MCF-7, and MCF-7 ADR) were higher than that against normal cells (NIH/3T3). Based on the characteristic of Lap, Chen et al. developed a pH/ROS dual-responsive iron-containing nanomedicine (**Figure 3A**) [46]. In this nanomedicine, Lap was encapsulated into polymeric micelles that assembled from a pH-responsive polymer, a ROS-responsive DOX-based polyprodrug. In intracellular acidic environment, Lap will be first released due to pH-triggered disassembly of the nanomedicine. Through iron-catalyzed Fenton reaction, the hydrogen peroxide produced by Lap will be transformed to hydroxyl radicals, which further cleave the thioketal linker between DOX and polyprodrug to release active DOX. Therefore, chemo/chemodynamic combination therapy was achieved by the cascade of hydroxyl radical generation and DOX release. Glucose oxidase (GOD), an enzyme that can convert oxygen and glucose into hydrogen peroxide and glucose acid, is also widely used to develop multifunctional nanomedicine [47, 48]. Ge's group has developed a series of GOD-based nanosystems for prodrug activation [49, 50]. For example, a GOD-encapsulated nanoreactor self-assembled from amphiphilic polyprodrug was prepared for oxidation/chemotherapy (**Figure 3B**) [49]. In acidic tumor environment, due to the permeability change of the nanoreactor membranes, glucose can diffuse into the nanoreactor and generate hydrogen peroxide under the catalysis of GOD. The high level of hydrogen peroxide will further trigger the cleavage of oxalate bonds and activate the polyprodrug, releasing active CPT. Therefore, this nanoreactor combines oxidation therapy and chemotherapy to inhibit tumor growth.

Hypoxia-triggered prodrug activation

In most solid tumors, hypoxia is a typical characteristic [51, 52]. Some ROS generation strategies, such as type II PDT and GOD-mediated catalytic process, need to further consume tumor oxygen to produce singlet oxygen or hydrogen peroxide [53]. The exacerbated hypoxia of tumor environment can also be used as a stimulus to activate hypoxia-responsive nanomedicines. Therefore, the combination of ROS-generating agents and hypoxia-activatable prodrugs is a promising approach to achieve enhanced cancer therapy.

One type of hypoxia-activatable prodrug is one that contains hypoxia-sensitive linkers. Xie et al. developed a hypoxia-activated self-immolative PTX dimer (PTX_2-Azo) by conjugating two PTX molecules through an azobenzene (Azo) linker (**Figure 4A**) [54]. The PTX_2-Azo was encapsulated in the NP self-assembled from chlorin e6 (Ce6)-containing amphiphilic copolymer, obtaining Ce6/PTX_2-Azo NP. Attributing to the passive targeting effect, the Ce6/PTX_2-Azo NP with a size of approximately 100 nm can effectively accumulate in tumor tissue. Upon laser irradiation, the encapsulated photosensitizer Ce6 will consume inherent oxygen and generate singlet oxygen to induce cell apoptosis. Due to the PDT-aggravated hypoxia, the Azo linker of PTX_2-Azo prodrug will be cleaved by reductases. Then the active PTX will be released through a cascade elimination reaction. Through the combination of PDT and prodrug activation, excellent antitumor efficacy can be achieved.

In another study, Pu's group reported a nanoprodrug (denoted as SPNpd) for PDT and hypoxia-activated drug release [55]. The SPNpd was self-assembled from a drug-conjugated amphiphilic semiconducting polymer. Bromoisophosphoramide mustard intermediate (IPM-Br), a chemotherapeutic drug, was conjugated to the SPNpd by using a hypoxia-cleavable linker (**Figure 4B**). In this system, the light-responsive semiconducting polymer was used as a photosensitizer, which can produce ROS under 808-nm light irradiation. Meanwhile, with the consumption of oxygen, the hypoxia of tumor exacerbated. In such a hypoxic condition, the linker between IPM-Br and the polymer will be cleaved by nitroreductase-catalyzed reduction, resulting in hypoxia-activated IPM-Br release. The activity will further induce DNA crosslinking and subsequent cellular apoptosis.

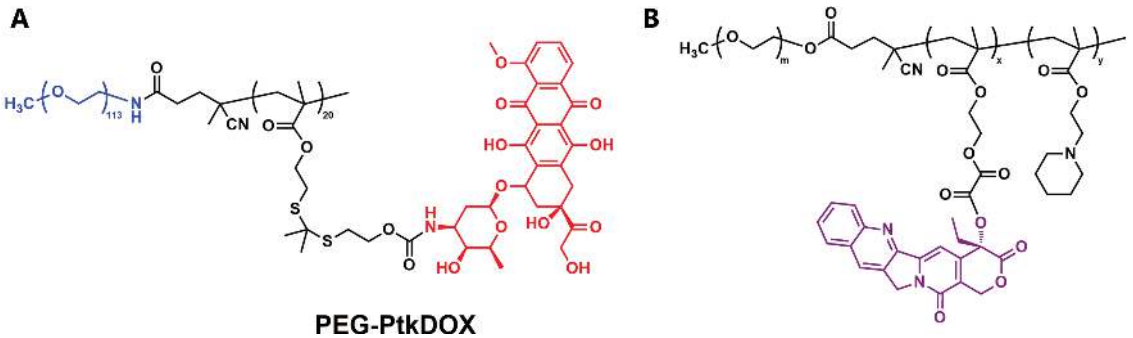

Figure 3 (A) Chemical structure of PEG-PtkDOX. (B) Chemical structure of ROS-responsive polyprodrug.

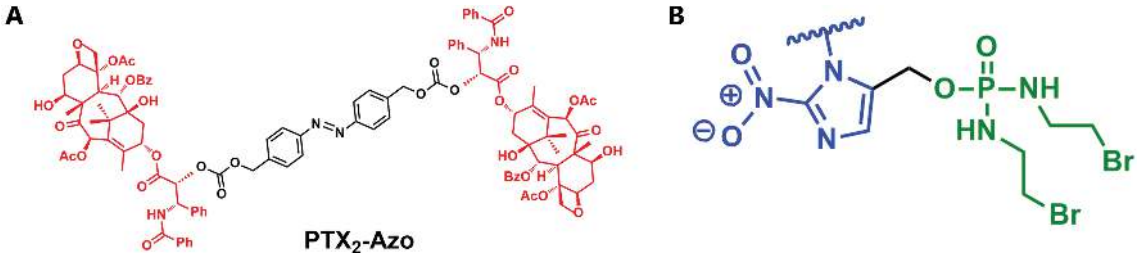

Figure 4 (A) Chemical structure of PTX_2-Azo. (B) Chemical structure of hypoxia-responsive prodrug.

Therefore, the SPNpd can realize synergistic photodynamic/chemotherapy and effective inhibition of tumor growth.

Another type of hypoxia-activatable prodrug mainly contains quinone-based prodrugs and N-oxide prodrugs that show little toxicity in normoxic condition and high toxicity in hypoxic condition. Among the prodrugs, TPZ is a widely studied one. In hypoxic condition, TPZ can be converted into toxic radicals through bioreduction (**Figure 5**) [56]. Therefore, the development of hybrid nanosystems that combine TPZ and photosensitizer represents a promising way to realize combination therapy. Porphyrinic metal-organic framework (MOF), which self-assembled from metal ion and porphyrin photosensitizer through coordination interactions, has attracted much attention. Porphyrinic MOF can be used not only as a nanophotosensitizer for PDT, but also as a nanocarrier for delivering other therapeutic agents. Li et al. reported a TPZ-loaded core–shell upconversion nanoparticle in porphyrinic MOFs (TPZ/UCSs) for combination therapy [57]. Under near-infrared (NIR) light irradiation, the upconversion nanoparticle core will convert the NIR light to visible light to activate photosensitizer in MOF shell, generating $^1O_2$ efficiently. Furthermore, PDT-aggravated tumor hypoxia will activate the pharmacological activity of encapsulated TPZ, enabling combinational photodynamic/chemotherapy. This study provides a promising nanoplatform in fighting tumor through the integration of NIR-triggered ROS generation and hypoxia-triggered prodrug activation.

The hypoxia-responsive prodrugs have also been combined with GOD to develop nanomedicine [58, 59]. Wu et al. constructed a hybrid nanoreactor (denoted as HGTFT) composed of human serum albumin (HSA), GOD, TPZ, Fe^{3+} and tannic acid (TA) for cascade chemo-chemodynamic therapy [60]. In cancer cells, GOD will first consume glucose and oxygen for starvation therapy, resulting in the production of hydrogen peroxide and aggravated hypoxia. Through TA-accelerated Fenton reaction, the hydrogen peroxide will react with iron ions to produce highly toxic hydroxyl radicals for chemodynamic therapy. Meanwhile, the hypoxic environment will activate TPZ to generate BTZ• for chemotherapy. The in vitro and in vivo results demonstrated excellent biosafety and enhanced anticancer activity of the HGTFT nanoreactor. Therefore, this nanoreactor has great potential for clinical applications.

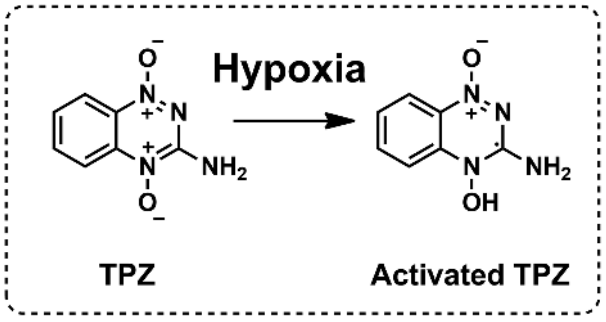

Figure 5 Chemical structures of TPZ and activated TPZ.

Cascade of prodrug release and activation

As we discussed above, the PDT process will lead to two consequences, high ROS level and aggravated hypoxia, both of which can be used for drug release and prodrug activation. In order to make full use of these two consequences, Sun and colleagues developed a nanomedicine that combines ROS-triggered prodrug release and hypoxia-triggered prodrug activation [61]. As shown in **Figure 6**, two types of heterodimeric dimers that based on hypoxia-responsive prodrug PR104A and photosensitizer PPa were synthesized. The PR104A and PPa were conjugated via a ROS-sensitive thioether or thioketal linkage. Then the heterodimeric dimers self-assembled to form prodrug-NPs with a dense intermolecular-packing structure. Under laser irradiation, the thioether or thioketal linkages between PPa and PR104A will be cleaved because electrons can be transferred from

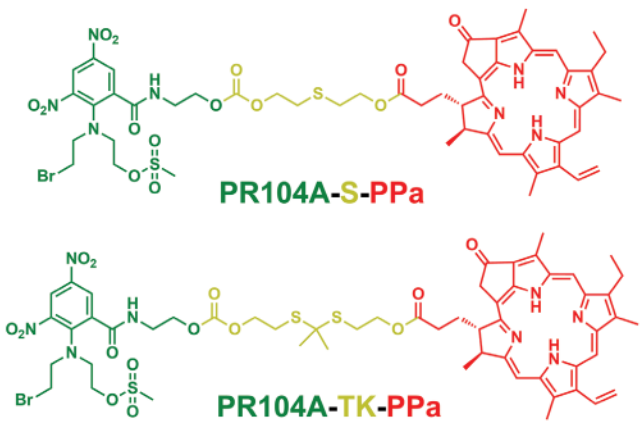

Figure 6 Chemical structures of PR104A-S-PPa and PR104A-TK-PPa.

PPa to the sulfur atoms via photoinduced electron transfer. Therefore, the PR104A prodrug will be released, causing disassembly of prodrug-NPs. As the ACQ effect was relieved, the PPa will efficiently consume oxygen and produce singlet oxygen to further promote the PR104A release. Meanwhile, the hypoxic condition caused by oxygen consumption will facilitate the activation of hypoxia-sensitive PR104A to realize DNA damage.

Conclusion and outlook

Compared with normal tissue, tumor tissue has unique structural and metabolic characteristics, such as weak acidic microenvironment, hypoxia condition, high ROS level, and overexpression of specific enzymes. Based on these special characteristics, prodrugs that can be activated in tumor site exhibit great potential in antitumor therapy. With the developments of stimuli-sensitive moieties, various prodrug and polyprodrug systems have been designed and applied in cancer treatments. However, the selectivity of generally used pH- and GSH-activated prodrugs is still limited. Many ROS generation strategies, such as PDT, can specifically consume tumor inherent oxygen and generate ROS, resulting in amplified ROS level and aggravated hypoxia. In recent years, nanomedicines that integrate ROS generation strategies with ROS- or hypoxia-responsive prodrugs have been developed. Upon accumulation in tumor tissue, the nanomedicines will first generate ROS in tumor site, which can not only cause cell death directly, but also activate prodrugs to improve therapeutic efficiency. Therefore, these nanomedicines show great potential to realize combination therapy with improved selectivity.

In this review, we summarized recent advances of the integration strategy. Although significant progress has been made in the design and application of ROS-responsive and hypoxia-responsive prodrugs, there are still some obstacles and challenges. For example, the efficiency of the first stage (ROS generation) will significantly affect the effectiveness of second stage (prodrug activation). Particularly, this strategy is difficult to apply to the treatment of hypoxic tumors. Furthermore, in some systems, the prodrug activation process needs to consume ROS, resulting in unsatisfactory combination treatment outcome. Therefore, for the future research, more efforts should be put toward to address these issues. In addition, ROS generation can also be triggered by engineered bacteria, which provided an opportunity for interdisciplinary integration.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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