Recent Advances of D-α-tocopherol Polyethylene Glycol 1000 Succinate Based Stimuli-responsive Nanomedicine for Cancer Treatment

Article · April 2020

DOI: 10.1007/s11596-020-2185-1

6 authors, including:

Songwei Tan
Huazhong University of Science and Technology
50 PUBLICATIONS **1,838** CITATIONS

SEE PROFILE

Current Medical Science
DOI https://doi.org/10.1007/s11596-020-2185-1
40(2):218-231,2020

Recent Advances of D-α-tocopherol Polyethylene Glycol 1000 Succinate Based Stimuli-responsive Nanomedicine for Cancer Treatment*

Yang GUAN[1], Lin-yan WANG[1], Bo WANG[1], Mei-hong DING[1], Yu-ling BAO[2#], Song-wei TAN[3#]
[1]*Academy of Chinese Medical Sciences, Zhejiang Chinese Medical University, Hangzhou 310053, China*
[2]*Department of Pharmacy, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China*
[3]*School of Pharmacy, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China*

Summary: D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) is a pharmaceutical excipient approved by Chinese NMPA and FDA of USA. It's widely applied as a multifunctional drug carrier for nanomedicine. The advantages of TPGS include P-glycoprotein (P-gp) inhibition, penetration promotion, apoptosis induction *via* mitochondrial-associated apoptotic pathways, multidrug resistant (MDR) reversion, metastasis inhibition and so on. TPGS-based drug delivery systems which are responding to external stimulus can combine the inhibitory functions of TPGS towards P-gp with the environmentally responsive controlled release property and thus exerts a synergistic anti-cancer effect, through increased intracellular drug concentration in tumors cells and well-controlled drug release behavior. In this review, TPGS-based nano-sized delivery systems responsive to different stimuli were summarized and discussed, including pH-responsive, redox-responsive and multi-responsive systems in various formulations. The achievements, mechanisms and different characteristics of TPGS-based stimuli-responsive drug-delivery systems in tumor therapy were also outlined.
Key words: D-α-tocopherol polyethylene glycol 1000 succinate; stimuli-responsive; nanomedicine; P-glycoprotein; cancer

D-α-tocopherol polyethylene glycol 1000 succinate (TPGS, fig. 1), formed by esterification of vitamin E succinate (VES) and polyethylene glycol (PEG), is a water-soluble derivative of natural vitamin E (VE). TPGS has an amphiphilic structure consisting of a lipophilic alkyl tail (VE) and a hydrophilic polar head (PEG). It is commonly used in drug carriers due to the good biocompatibility and preferable physicochemical properties[1–3]. TPGS has been approved as a pharmaceutical excipient by Chinese NMPA and FDA of USA. With the development of research on TPGS, many studies showed that TPGS-based anti-tumor nanomedicine exhibited high drug entrapping efficiency, long circulation time in body and good oral bioavailability[4–6]. More importantly, TPGS is also an efficient P-glycoprotein (P-gp) inhibitor. By binding to the non-transporting active site on P-gp, resulting in a conformational change and dysfunction of the original transportation of the P-gp[7, 8], and then TPGS effectively reduces the efflux of drug from tumor cells. The further study confirmed that TPGS and relevant derivatives could bind to the ATP active site of the P-gp nucleotide binding domains, which blocked the bond of ATP enzyme and restricted the hydrolyzation of ATP, subsequently cut off the energy supply of P-gp to reduce the substrate efflux and finally realized multidrug resistance (MDR) reversal[9–11]. Moreover, TPGS could be a potential inhibitor towards mitochondrial function. TPGS can reduce ATP consumption (ΔRLU) and decrease the mitochondrial membrane potential (MMP). It was proposed that TPGS could not only reduce ATPase activity, but also affect mitochondrial function to inhibit P-gp[12–14]. This phenomenon has also been confirmed in some nano-drug systems based on TPGS as well. Wang *et al*[15] showed that TPGS could affect mitochondrial function through causing damage to the double-membrane structure of mitochondrial and disturbing the micro-environment of P-gp jet pump by reducing ATP production. And another study[16] has shown that TPGS was able to trigger mitochondrial apoptosis, which is helpful for inhibiting P-gp in tumor

Yang GUAN, E-mail: guanyang104@126.com
#Corresponding authors, Yu-ling BAO, E-mail: yulingbao@hotmail.com; Song-wei TAN, E-mail: tansw@hust.edu.cn
*This study was supported by the National Natural Science Foundation of China (No. 81871473) and the Natural Science Foundation of Zhejiang Chinese Medical University (No. 2018ZZ11).

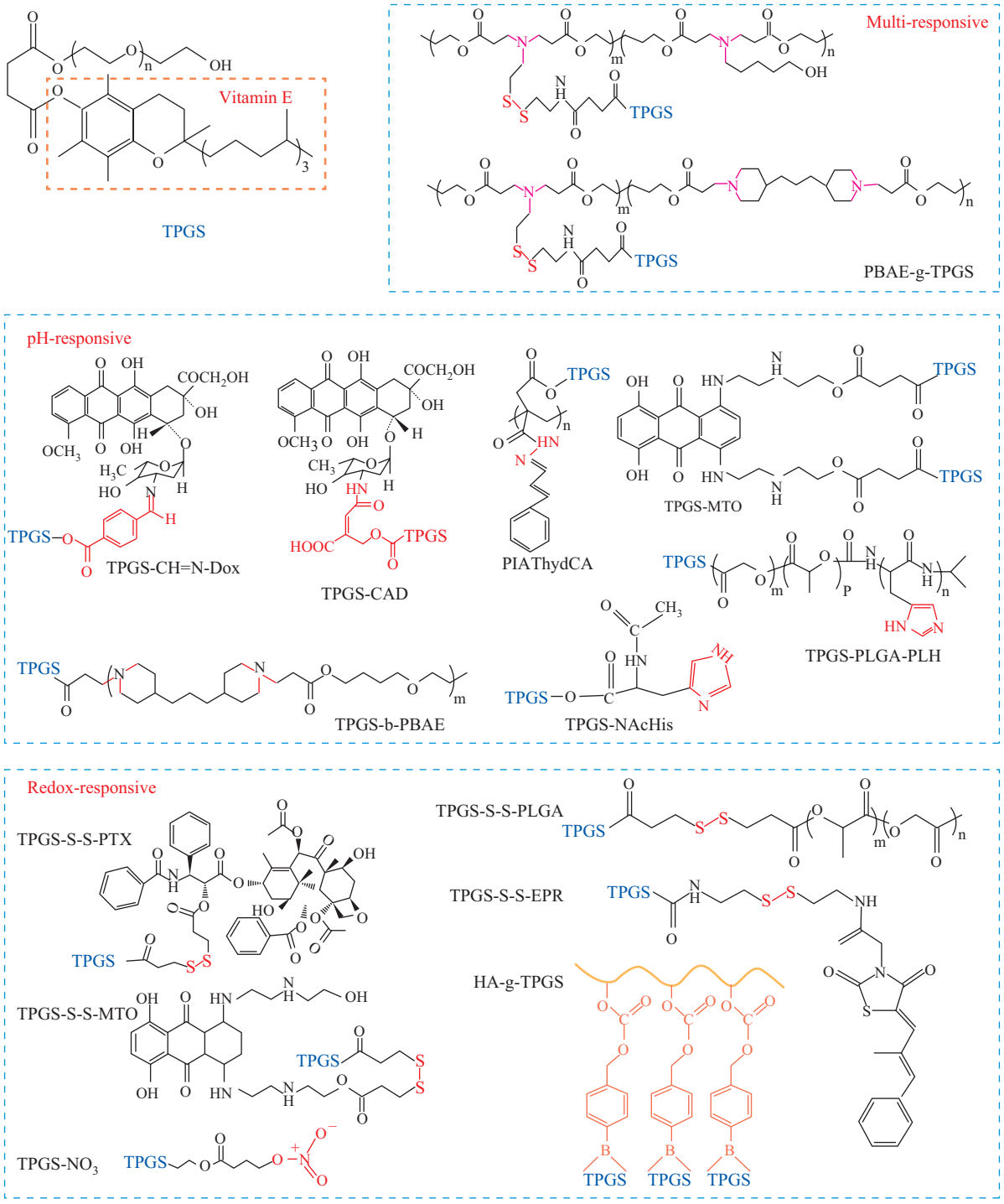

Fig. 1 Chemical structure of TPGS based stimuli-responsive copolymers

cells. Therefore, the synergistic treatment of TPGS and anticancer drugs has a good prospect. TPGS can be utilized as a carrier for drug delivery, and can also reduce the efflux effect of chemotherapeutical drugs by inhibiting P-gp in tumor cells, so as to maintain a high level of intracellular drug concentration and then improve the antitumor efficiency. Moreover, TPGS can also enhance the treatment efficacy of MDR tumors through mitochondrial apoptosis pathway and even inhibit the metastasis, which benefits to the application of TPGS in anti-tumor treatment.

Polymers are excellent drug carriers. They have good biological compatibility, nice stability in the tissue environment, high loading capacity of drugs[17–19]. Moreover, their structure is flexible and can be designed to realize certain functions as needed, such as biodegradation, stimuli-responsibility and targeting modification[20, 21]. Among these, stimuli-responsive nano-drug system is widely applied in the field of anti-tumor, which can solve the problems of biodistribution,

insufficient drug release and side effects in the delivery of traditional chemotherapeutics[22–25]. The combination of stimuli-responsive system and TPGS retained the advantages of the both, and thus attracted considerable attention[1, 2, 5]. In general, such systems exist stably in the normal tissue environment, while at the tumor site they release a sufficient number of drugs in response to the tumor microenvironment. Then the therapeutic effect can be enhanced because of the combined effect of the multifunction of TPGS and the burst drug release. To achieve this goal, pH-responsibility, redox-responsibility and/or other stimuli-responsibility were introduced into TPGS-based nanomedicine. Here, we reviewed the recent progresses of stimuli-responsive drug delivery systems based on TPGS for anti-tumor, which provided a useful reference for the future development of this field (table1).

1 PH-RESPONSIVE DRUG DELIVERY SYSTEM BASED ON TPGS

The pH-responsive drug delivery system is the most commonly used vehicle. The pH in normal human tissues is generally neutral with a value of approximately 7.4. However, the environment in tumor tissue is usually acidic due to the lactic acid produced by tumor cells *via* anaerobic glycolysis[26]. Generally, the intercellular substance of tumor is weakly acidic with a pH value between 6.5 and 6.8[27, 28]. Furthermore, after endocytosis by cancer cells, the pH value of endosomes/lysosome is 6.0–4.0[29, 30]. The difference in pH value can be used as a switch to trigger the rapid disassembly of drug-loaded system. At the same time, owing to the function of TPGS, the efflux of released drugs is greatly suppressed, and a large number of drugs can accumulate in the tumor cells to improve the therapeutic effect, subsequently.

TPGS can be used directly as a drug carrier as well as modified by other materials. It is an efficient and simple form of pH-responsive drug delivery system based on TPGS by directly mixing TPGS into the pH-responsive drug-loaded micelles or nanoparticles (NPs). Yu *et al*[13] prepared a pH-responsive di-block copolymer, poly (ethylene glycol)-block-poly (2-(diisopropylamino) ethyl methacrylate) (PEG-b-PDPA). After mixing with TPGS, PEG-PDPA/TPGS micelles formed for encapsulation of Doxorubicin (DOX) into the core of micelle under neutral condition. When the micelles were taken up by cells, the protonation of the di-isopropyl-substituted tertiary amino groups would happen in the acidic environment of early endosomes, which led to the dissociation of micelles and release of DOX. Meanwhile, TPGS can reduce the mitochondrial transmembrane potential and synergistically improve the cytotoxicity of DOX. PDPA/TPGS micelles reduced the IC50 value of DOX in resistant cells MCF-7/ADR by 6 times. Animal experiments showed that DOX-loaded PDPA/TPGS micelles (PDPA/TPGS@DOX) significantly inhibited the growth of orthotopic MCF-7/ADR tumor in a nude mouse model compared with free DOX. Similarly, Zhou *et al*[31] reported a PEG-poly(β-amino esters) (PEG-PBAE)/TPGS hybrid micelle. Realizing P-gp inhibition *via* disrupting mitochondrial function and lowering ATP levels, DOX-loaded hybrid micelle system showed more cytotoxicity to MCF-7/ADR cells than free DOX. TPGS can also optimize the performance of nano-carrier in drug delivery. Hung *et al*[32] developed a nano-carrier (NHTPNs) comprising PLGA as the hydrophobic core and N-acetyl histidine was modified with TPGS (NAcHis-TPGS) as the shell. The surface charge of the system can be changed with the variation of the acidity of the tumor extracellular environment. The photothermal agent, indocyanine green (ICG) and the chemotherapeutic drug, DOX were selectively delivered to the tumor site. Experimental results showed that when the pH of the external environment changed from 7.4 to 5.0, the ζ-potential of nano-carriers would change from negative to neutral or positive value due to the protonation enhancement of the imidazole group of the NAcHis-TPGS fragment, which increased the affinity of ICG/DOX loaded NHTPNs towards tumor cells, then more drug-loaded NPs were taken up by tumor cells to achieve passive targeting. Fluorescent images also showed that DOX delivered by NHTPNs was more concentrated in the cytoplasm and nucleus of tumor cells, whereas free DOX was difficult to enter the cells. On the other hand, the increase of positive charge on the surface of NHTPNs can also promote the absorption and uptake of nano-carriers by macrophages in the acidic microenvironment of tumor cells, so that the NPs can penetrate into deep tumor hypoxic condition, which is a tough task for ordinary nano-carriers. In addition, ICG/DOX-loaded NHTPNs had a good image-guided photothermal capability, which can induce extensive apoptosis, and significantly inhibit tumor growth and recurrence. A mixed micelle system consisting of TPGS1000, TPGS2000 and α-TOS was developed for DOX encapsulation[14]. The loaded DOX showed a pH-dependent release, which was about 4 times higher under acidic condition (pH=5.5) than that under neutral condition (pH=7.4). Meanwhile, due to the P-gp inhibition function of TPGS, intracellular drug accumulation increased. The anti-tumor efficiency of DOX-loaded mixed micelles was 45 times higher than that of free DOX *in vitro* (in MCF-7/ADR cells), and DOX-loaded mixed micelles showed reduced cardiotoxicity and hepatotoxicity *in vivo* comparing with the free DOX. We also applied TPGS as a stabilizer to improve the stability of a novel pH-responsive NP system composed by poly (β-amino ester)-g-β-cyclodextrin (PBAE-g-β-CD)[33]. After the

Table 1 TPGS based formulations used for cancer therapy

Responsibility	Formulations	Drug	Highlights	Ref.
pH-response	PEG-PDPA/TPGS hybrid micelle	DOX	Reduce the mitochondrial transmembrane potential and synergistically improve the cytotoxicity of DOX, reduce the IC50 value of DOX in resistant cells MCF-7/ADR by 6 times	[13]
	PEG-PBAE/TPGS hybrid micelle	DOX	Disrupt mitochondrial function and lower ATP levels, more cytotoxicity to MCF-7/ADR cells than free DOX	[31]
	PLGA/NAcHis-TPGS hybrid micelle	ICG and DOX	Deliver DOX to nucleus of tumor cells, deep penetration in tumor tissue	[32]
	TPGS1000, TPGS2000 and α-TOS mixed micelle	DOX	45 times higher than free DOX *in vitro* (in MCF-7/ADR cells), reduce cardiotoxicity and hepatotoxicity *in vivo*	[14]
	PBAE-g-β-CD/AD-TPGS NPs	DOX and ADD	Program drug release and the tumor drug resistance reversion	[33]
	DOX-TPGS prodrug/ (cRGD)-DSPE-PEG hybrid micelle	DOX	Induce apoptosis by mitochondrial depolarization, enhance the growth/metastasis inhibition to melanoma B16F10	[38]
	CAD-TPGS prodrug	DOX and Ce6	Improve therapeutic efficacy and reduce system toxicity	[39]
	PIAThydCA prodrug	CA	Increase intracellular ROS levels and induce apoptosis of MCF-7 cells through the mitochondrial pathway, no toxicity to normal cells	[40]
	TPGS-b-PBAE	DTX	P-gp inhibition and significantly enhance cytotoxicity against the drug-resistant human ovarian cancer	[45]
		DOX and CUR	Better therapeutic effect on HCC inhibition due to the proapoptotic effect of DOX and anti-angiogenesis function of CUR, high accumulation in tumor cells and long retention time	[46]
	PLH-PLGA-TPGS	DOX	Concentrate in lysosomes and have a burst release of DOX, more destructive to DOX-resistant McF-7/ADR cells than free DOX	[47]
	Cu-MSNs-DOX/TPGS.	DOX	Keep high drug concentration in cells, reduce the MDR expression, realize multi-drug synergistic therapy	[50]
	MSNs-DOX@PDA-TPGS	DOX	Significantly increase the release of DOX in late endosome and lysosome, overcome MDR	[51]
	MTO-TPGS prodrug/FA-TPGS mixed micelles	MTO	Increase the uptake of MCF-7 cells, significantly increase the accumulation of MTO *in vivo*, enhance the anti-tumor effect	[52]
	HDP/FA-TPGS2k	PTX	Higher anti-tumor activity on PTX-resistant MCF-7 breast cancer cells, synergy of pH-dependent release, TPGS-mediated P-gp inhibition and FA receptor-mediated endocytosis	[53]
Redox-response	TPGS-SS-PTX prodrug	PTX	Accelerate PTX release rate in tumor cells, better effect of killing the drug-resistant tumor cells than Taxol	[62]
	TPGS-MTO prodrug	MTO	Significantly inhibit the growth of drug-resistant breast tumor cells ATP activity depletion caused by the interaction between mitochondria and TPGS	[63]
	EPR-SS-TPGS/TPGS-B6/DOX hybrid micelles	DOX and EPR	Prolong the circulating half-life of both drugs, increase the bioavailability of the drugs in the tumor site, significantly down-regulate CD44 receptor level, reduce the cardiac toxicity	[64]
	MPEG-SS-2SA/TPGS mixed micelles	PTX	Significantly inhibit the activity of the mitochondrial respiratory complex Ⅱ, reduce ATP levels, prevent the efflux of PTX in cells	[65]

(Continued to the next page)

(Continued from the last page)

Responsibility	Formulations	Drug	Highlights	Ref.
Redox-response	TPGS-ss-PLA, cRGD	PTX	Accelerate PTX release under the reductive condition of tumor cells, with preferable curative effect on PTX-resistant tumor cells	[66]
	LA-PLGA-TPGS/DSPE-PEG	DTX	Significantly increase the uptake of DTX by tumor cells and inhibit cell proliferation	[67]
	TNO_3	DOX	Being stable in physiological conditions but release NO fast in cancer cells	[68]
	TPGS-SS-PTX/ TPGS nitrate mixed micelles	PTX	"Self-promoted delivery" function, increase the vascular permeability of tumor, blood perfusion and vascular density, promote the accumulation of micelles in the tumor	[69]
	TPGS-NO	DOX-ADD	Depress P-gp by inducing mitochondrial dysfunction of TPGS and inhibiting mitochondria of ADD, with significant effect on inhibiting tumor growth and metastasis of MCF7 resistant cells	[70]
	TPGS-s-PTX/TPGS-sccs-PTX	PTX	Increase tumor-specific ROS signal by inhibiting the mitochondrial respiratory complex Ⅱ, maintain a high ROS level to induce the rapid and complete release of drug, induce mitochondria-mediated apoptosis *via* the ROS/Cyt C/caspase-9/3 pathway	[71]
	TBH	DOX	Expand the triggering and regeneration mechanism of ROS, tumor targeting, and MDR reversal ability, significantly inhibit the tumor growth of MCF-7/ADR tumor-bearing nude mice	[72]
Enzyme-response	TGK/TPGS hybrid micelles	PTX	Double uptake of HT1080 cells compared to nonsensitive system under the MMP-2/9 environment, good targeting and accumulation capacity	[73]
Temperature-response	TPGS/PID118-b-PLA71 mixed micelles, anti-GD2 antibody	DOX	Lead to more drug release and enhance cell endocytosis in NB cells, with good activity against NB *in vitro*	[74]
	DOC-NCS/TPGS/PF127 hydrogel	DTX	Higher inhibition on growth of SMMC-7721/RT cells, an *in situ* local drug depot with P-gp inhibition capability, good therapeutic effect on drug-resistant solid tumors	[75]
pH and redox dual response	C32-g-TPGS	PTX	With a burst release of PTX in acidic and reductive environment, greatly enhance the cytotoxicity against drug-resistant cells (A2780/T)	[81]
	PBAE-g-TPGS/F127-FA hybrid micelles	PTX	Increase the cell uptake, heighten toxicity to tumor cells, inhibit drug efflux, with good effect to suppress the growth of drug-resistant tumor	[82]
	LTMSNs/TPGS NPs	DOX	Better uptake efficiency, greater cytotoxicity and higher intracellular accumulation in drug-resistant MCF-7/ADR cells	[83]
Redox and NIR photothermy dual response	MSNs-Cy/TPGS NPs	DOX	Combine the effect of hyperthermia and MDR inhibition, enhance anti-tumor activity as compared with single treatment strategy	[84]

coupling of TPGS and adamantoic acid (AD), the resultant AD-TPGS could insert into β-CD through host-guest interaction, which could reduce the surface potential of particles and increase the stability of the system. Such composite system could co-load and realize programmed release of DOX and adjudin (a mitochondrial function inhibitor) so as to achieve higher tumor killing effect, reduce the required drug dose and overcome the tumor drug resistance.

Polymers are usually used to bond with drugs to form inactive precursors, known as prodrugs[34]. The active drug can be dissociated under external signal stimulation *in vivo*. TPGS is widely used as prodrug substrate, with the advantages of good self-assembly effect, long circulation time and increased cell uptake[35–37]. The design of pH-responsive breaking chemical bonds in the prodrug can make drug release faster and more accurate. We synthesized a safe and effective pH-responsive prodrug where DOX and TPGS were conjugated by Schiff base bond[38]. This prodrug self-assembled with PEGylated lipid to form a hybrid micelle system. When the hybrid micelle entered into tumor cells by endocytosis, DOX and TPGS were rapidly released in the low pH environment of tumor cells due to the hydrolysis of Schiff base bond. The released TPGS not only reduced the drug efflux, but also induced apoptosis caused by mitochondrial depolarization. The tumor targeting ability of nano-drug was further enhanced by surface modification of hybrid micelles with targeted integrin ligand cRGD. As a result, the hybrid micelles were demonstrated to enhance the growth/metastasis inhibition to melanoma B16F10. Because of the self-assembly ability, polymer prodrug could also be a carrier to deliver other drugs. Hou *et al*[39] combined *cis*-aconitic anhydride-modified doxorubicin (CAD) with TPGS to prepare a pH-responsive anti-tumor prodrug NPs (TCAD NPs) by self-assembling, and then photosensitizer chlorin Ce6 (Ce6) was loaded into the prodrug NPs to fabricate a pH-responsive tumor near-infrared fluorescence imaging and chemo-photodynamic combination therapy system (TCAD@Ce6 NPs). Due to the hydrolysis of acid-responsive amide bonds under the acidic condition, accelerated release of both DOX and Ce6 occurred in the simulated tumor microenvironment (pH=6.5), and more drugs released at pH5.5 which was close to the value in cell lysosome. In a neutral environment, Ce6 was concentrated in the core of NPs. This system kept a low fluorescence intensity to maintain low phototoxicity in the blood circulation because of self-quenching effect. However, under the acidic environment in the tumor, the NPs released more Ce6, which increased the fluorescence intensity and enhanced the phototoxicity in the tumor cells. TCAD@Ce6 NPs realized a pH-triggered chemo-photodynamic combination therapy, achieved an improved therapeutic efficacy and reduced system toxicity compared with the positive controls. Designing prodrugs based on multiple pathways according to the tumor microenvironment can also enhance anti-tumor efficacy. Dong *et al*[40] connected TPGS to the homopolymer of itaconic acid *via* ester bond to obtain an amphiphilic polymer, PIAT, which was linked by cinnamaldehyde (CA) through pH-responsive hydrazone bond to establish prodrug PIAThydCA. The system was stable in the neutral environment of normal cells, but released CA due to the hydrazone bond breaking in acidic tumor environments, as well as lysosomes and endosomes. The released CA and TPGS synergistically increased intracellular reactive oxygen species (ROS) levels and induced apoptosis of human breast cancer cells MCF-7 through the mitochondrial pathway. Moreover, PIAThydCA and PIAT did not show toxicity to normal cells L929, indicating the good specificity of this system towards tumor.

Copolymers of TPGS with other monomers can also be used as smart drug carriers. Generally, these copolymers contained primary, secondary, and/or tertiary amines[41]. In neutral environment, the pH-responsive segments performed as hydrophobic materials, which is suitable to encapsulate the hydrophobic drugs. Under weak acidic conditions, the main chain protonates, which break endosomes through the "proton sponge" effect and achieves the rapid release of the entrapped drugs[42–44]. We first synthesized a novel copolymer TPGS-b-PBAE (TP) for loading Docetaxel (DTX) to realize a rapid release of DTX at pH5.5[45]. The TP copolymer inhibited P-gp and significantly enhanced cytotoxicity against the drug-resistant human ovarian cancer A2780/T. Zhang *et al*[46] also used this delivery system (TPGS-b-PBAE) for the co-encapsulation of DOX and curcumin (CUR) to improve the release rates of DOX and CUR at acidic environment. The proapoptotic effect of DOX and anti-angiogenesis function of CUR generated the synergistic effect, which had a better therapeutic effect on hepatocellular carcinoma (HCC) inhibition. Specially, the TPGS fraction made the whole system to maintain a higher accumulation in tumor cells and a longer retention time, probably due to the extended circulating time of NPs. The efficiency of rapid drug release combined with P-gp inhibition was verified in many delivery systems. Li *et al*[47] prepared another TPGS-based pH-responsive copolymer, poly (L-histidine)-poly (lactide-co-glycolide)-TPGS (PLH-PLGA-TPGS), as a drug carrier. They examined the loading and intracellular release condition of DOX. Since protonation of the imidazole group in PLH rose below pH6.0, PLH-PLGA-TPGS NPs swelled in endosomes and lysosomes, and the sudden release of DOX triggered in tumor cells. Studies have shown that, after being internalized by MCF-7/ADR cells

for a certain period of time, most particles were concentrated in lysosomes, which accelerated the release of DOX because of the acidic conditions. In addition, compared to free DOX, the drug-loaded NPs were more destructive to DOX-resistant MCF-7/ADR cells, which effectively reversed the MDR effect.

Inorganic NPs another widely-used drug carriers[48, 49]. The surface modification of inorganic particles may improve the treatment efficacy of inorganic NPs. Kankala *et al*[50] designed copper-substituted mesoporous silica nanocarriers (Cu-MSNs) to load DOX. The Cu-MSNs framework was conjugated to DOX by a pH-responsive linker and coated with TPGS to obtain the monolayer vesicle. After endocytosis of tumor cells, DOX was largely released because of the breaking of coordination bonds between DOX and co-impregnated copper (II) in the mesoporous materials under the low pH of endosomes. TPGS kept the concentration of nano-drugs in cells at a high level by reducing the MDR presentation and inhibiting its function to realize the synergistic therapy. Binding through covalent bond allows TPGS to be more stably modified on the surface of the NPs to avoid loss during circulation compared to the coating alone. Cheng *et al*[51] encapsulated DOX in mesoporous silica NPs (MSNs), and then coated highly adhesive polydopamine (PDA) on the surface of MSNs-DOX through oxidative polymerization, finally conjugated TPGS-NH_2 to the PDA coated MSNs-DOX to obtain MSNs-DOX@PDA-TPGS by Michael addition reaction. Under normal physiological conditions (pH=7.4), PDA, attached to the surface of the NPs, was stable and effective to prevent drug release. When pH dropped to 5.0, the release of DOX increased significantly because the PDA coating partially degraded and fell off due to a decrease in pH value, which meant the "gate keeper" on the surface of the NPs was open and the cargo in NPs was free to be released consequently (fig. 2). Meanwhile, the same as other systems, TPGS was helpful for overcoming MDR and demonstrated a good antitumor effect.

Connecting the targeted ligands to the stimuli-responsive system through TPGS is an alternative way to achieve active targeting. For instance, Guissi *et al*[52] designed mitoxantrone prodrug (MTO-TPGS), connected folate (FA) with TPGS to obtain FA-TPGS, and finally produced the pH-responsive mixed micelles (MTO-FMCT). Both the initial release amount in the first 12 h and the cumulative release amount in the 40 h at pH5.0 were 100%–110% more than that at pH7.4. In addition, MTO-FMCT increased the uptake of MCF-7 cells through folate-mediated endocytosis, which significantly increased the accumulation of MTO *in vivo*, and enhanced the anti-tumor effect. Besides, the TPGS with ligand could realize multi-functionality with the P-gp inhibition of TPGS. Another example is paclitaxel (PTX) loaded dextran-g-PLGA-g-histidine (HDP)-FA-TPGS2k mixed micelles[53]. Due to the protonation of imidazole ring of the HDP copolymer in the mixed micelles, the PTX release of this system increased by 40% when pH decreased from 7.4 to 5.0. *In vivo* experiments confirmed that the mixed micelles had higher anti-tumor activity on PTX-resistant MCF-7 breast cancer cells than the free PTX, which may be related to the synergy of pH-dependent release, TPGS-mediated P-gp inhibition and FA receptor-mediated endocytosis.

2 REDOX-RESPONSIVE DRUG DELIVERY SYSTEM BASED ON TPGS

In addition to the difference in pH value, tumor cells have a specific redox microenvironment compared to normal cells. The concentration of

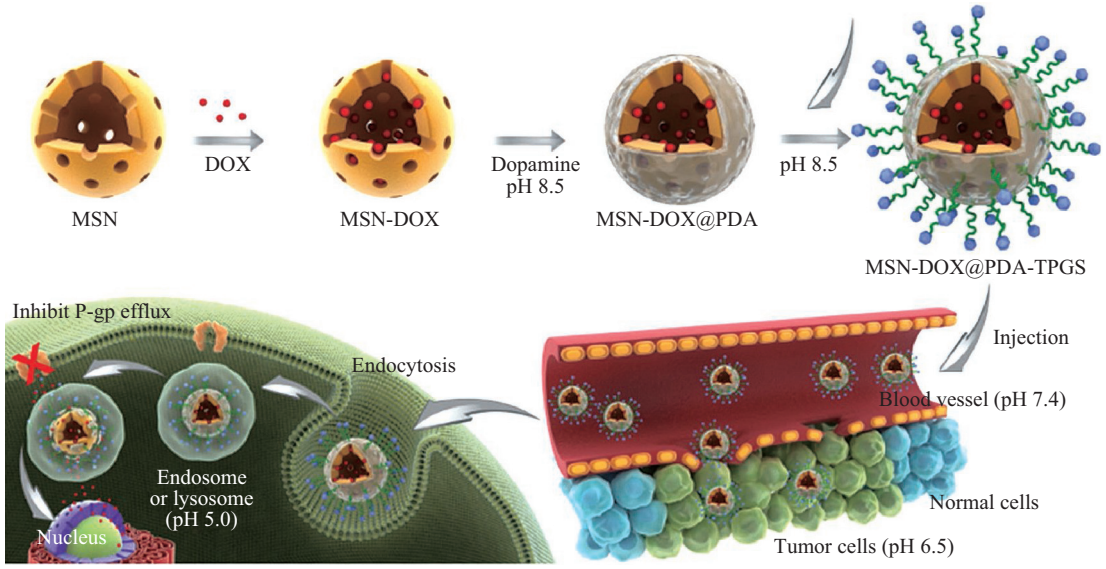

Fig. 2 Schematic illustration of pH-responsive doxorubicin-loaded MSNs-DOX@PDA-TPGS NPs to overcome MDR of tumor. Copyright 2020 from Wiley[51]

glutathione (GSH) in the intracellular fluid of tumor cells is at least 4 times higher than that in normal tissues (approximately 4 μmol/g *vs.* 1 μmol/g)[54, 55]. Besides, the growth of ROS in cells is associated with cancer, infection, inflammatory diseases, etc. In some tumor tissues, a high concentration of ROS was observed[56–58]. Based on the large difference of GSH/ROS concentrations inside and outside of tumor microenvironments, researchers designed a series of smart redox-responsive drug delivery systems. Among these, introducing the disulfide bond into the drug carrier is the most commonly used method[59–61]. In the presence of a certain amount of the reducing agents such as GSH and cysteine, disulfide bond breaks and promotes the drug release from the carrier.

We firstly reported a redox-responsive TPGS based prodrug, TPGS-SS-PTX, by connecting TPGS and PTX *via* dithiodipropionic acid[62]. This prodrug could self-assemble to form stable micelles with a diameter of about 140 nm in the physiological environment. However, under the condition of 10 mmol/L DTT (simulated tumor environment), the release rate of PTX was accelerated due to the cleavage of disulfide bond and thus PTX exhibited a better effect of killing the drug-resistant tumor cells than Taxol. Qiao *et al*[63] also synthesized disulfide bond containing TPGS-mitoxantrone (MTO) prodrug. When micelles were absorbed into the tumor cells, the MTO was rapidly released under the high concentration of GSH in the cells. Compared to free MTO, the TPGS-MTO prodrug micelle significantly inhibited the growth of drug-resistant breast tumor cells (MDA-MB-231/MDR), which was attributed to the ATP activity depletion caused by the interaction between mitochondria and TPGS. Banala *et al*[64] developed a redox-responsive hybrid micelle system to synergistically release different drugs. Epalrestat (EPR) was combined with TPGS to obtain a redox-responsive prodrug (EPR-SS-TPGS). TPGS-vitamin B6 (TPGS-B6) was also synthesized. Then EPR-SS-TPGS, TPGS-B6 and DOX were mixed in the appropriate ratio to form the hybrid micelles. In the presence of DTT, the release amount of DOX and EPR in the micelle system greatly increased compared to that in normal environment. TPGS prolonged the circulating half-life of both drugs and increased the bioavailability of the drugs in the tumor site. The mixed micelles significantly down-regulated CD44 receptor level, better suppressed tumor metastasis, and reduced the cardiac toxicity for the EPR and active target by promoting drug accumulation in tumor site.

Disulfide bonds can be conveniently bonded between materials to form polymer carriers. Dong *et al*[65] prepared a novel biodegradable amphiphilic polymer MPEG-SS-2SA which was synthesized through disulfide bonds between PEG monomethyl ether (MPEG) and stearic acid (SA), and prepared PTX loaded mixed micelles of MPEG-SS-2SA and TPGS. In a reductive environment (10 mmol/L DTT), a large amount of PTX was released within 24 h. In addition, owing to TPGS, mixed micelles could significantly inhibit the activity of the mitochondrial respiratory complex II, reduce ATP levels and effectively prevent the efflux of PTX in cells, thus showing the effect of MDR reversal of tumor cells. Zhang's group[66] connected TPGS and PLA by disulfide bond to form a copolymer, TPGS-SS-poly(lactide) (TPGS-ss-PLA), then prepared PTX-loaded NPs through solvent-emulsifying method with cRGD as the tumor targeting group. Under the reductive condition of tumor cells, PTX release was accelerated. The NPs had a preferable curative effect of PTX-resistant tumor cells with the cooperation of TPGS which inhibited drug efflux. Wang *et al*[67] prepared a core-cross-linked iRGD conjugated NP system based on lipoic acid modified TPGS-g-PLGA (LA-PLGA-TPGS) and DSPE-PEG respectively. Under reductive conditions (10 mmol/L DTT), the mixed micelles dissociated rapidly, thus triggering the release of the loaded DTX. The NPs significantly increased the uptake of DTX by tumor cells and inhibited cell proliferation consequently.

Nitrate is a redox-responsive group and quick nitric oxide (NO) release can be triggered by the GSH in tumor cells. Zhang's group synthesized TPGS nitrate (TPGS-NO_3) as a NO releasing system, which was stable in physiological conditions while released NO fast in cancer cells[68]. On this basis, we combined TPGS-SS-PTX and TPGS nitrate to obtain mixed micelles (TSP-TN) with the function of "self-promoted delivery"[69]. The mixed micelles could accumulate in the tumor through the EPR effect. After the endocytosis by the tumor cells, PTX and NO were rapidly released under a reductive environment, and NO could diffuse outside the tumor cells to exert bio-functions such as vasodilation and angiogenesis, thereby increasing the vascular permeability of tumor, blood perfusion and vascular density, and further promoting the accumulation of micelles in the tumor. TPGS inhibited P-gp and cooperated with PTX to overcome MDR (fig. 3). TSP-TN mixed micelles demonstrated a great potential to prevent tumor progression and proliferation by remodeling the tumor microenvironment. TPGS-NO was further used as a carrier for delivery of DOX-ADD (a conjugated compound of DOX and Adjudin linked by the hydrazone bond)[70]. Similar to TSP-TN, NO and TPGS cooperated to improve the accumulation and penetration of drugs in tumor tissues. Meanwhile, TPGS inhibited P-gp by inducing mitochondrial dysfunction; ADD was also a mitochondrial inhibitor that depressed P-gp activity. Therefore, this micelle had a significant effect on inhibiting tumor growth and metastasis of MCF7 resistant cells.

Other chemical bonds with redox-responsibilities

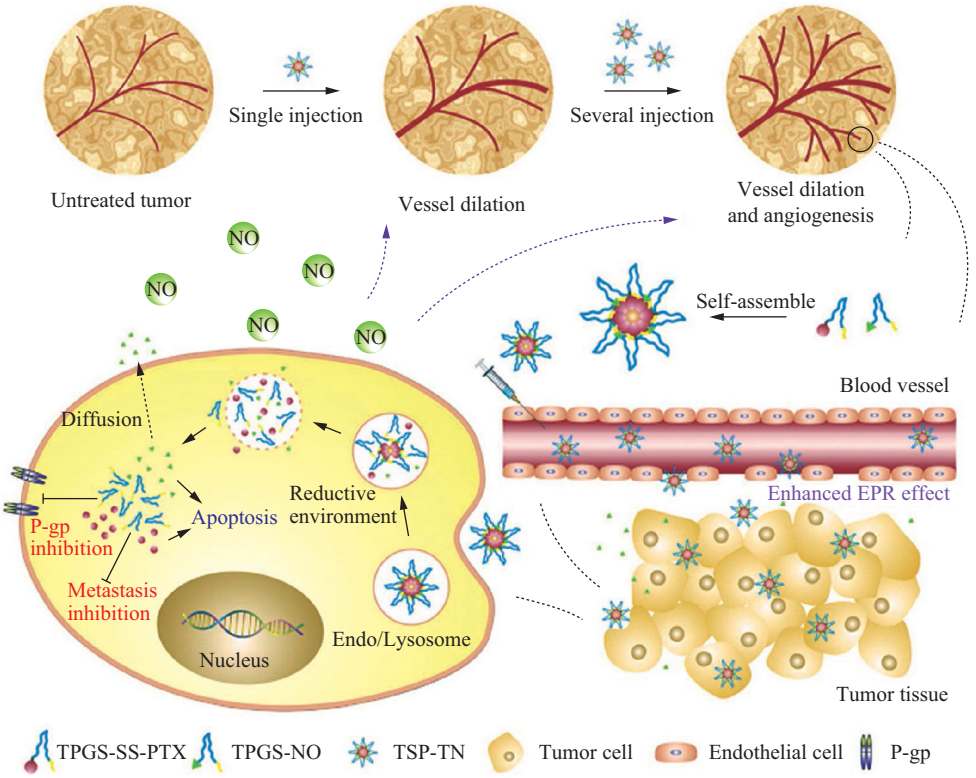

Fig. 3 Schematic illustration of the redox-responsive hybrid micelle system to enhance tumor therapy *via* drug co-delivery and self-promoted strategy. Copyright 2020 from Elsevier[69]

are designed in carrier construction. Zhang's group[71] combined TPGS1000 and PTX by single sulfide bond and disulfide bond respectively to obtain two kinds of dual redox-responsive prodrugs TPGS-s-PTX and TPGS-sccs-PTX, and then they self-assembled to obtain prodrug micelles TSP PMs and TSCS PMs. They found that TSP PMs and TSCS PMs were responsive to the two opposite stimuli of oxidation and reduction. In the environment of GSH and H_2O_2, the burst release of PTX occurred, and the PTX release amount of TSP PMs was larger than that of TSCS PMs. Besides, TPGS could increase tumor-specific ROS signal by inhibiting the mitochondrial respiratory complex Ⅱ, thereby establishing ROS-generated positive feedback effect, which could supplement the consumed ROS to maintain a high level of ROS, then induce the rapid and complete release of drug. The elevated ROS could also induce mitochondria-mediated apoptosis *via* the ROS/Cyt C/caspase-9/3 pathway, and reverse MDR by P-gp efflux inhibition. The influence on mitochondrial function of TPGS itself enabled it to control redox system in tumor cells. Su *et al*[72] synthesized a novel amphiphilic copolymer (TBH) by linking hyaluronic acid (HA) and TPGS through aryl borate ester. When TBH carrier entered tumor cells, the aryl borate degraded under the action of intracellular ROS. As a result, this system rapidly disintegrated into TPGS and HA, and the loaded drug DOX in the system released. The dissociated TPGS enhanced the drug retention effect to increase cytotoxicity. On the other hand, TPGS promoted ROS regeneration *via* mitochondrial pathway, which supplemented the consumption of ROS by TBH system. In addition, HA could improve the tumor targeting ability. The TBH-delivery system expanded the triggering and regeneration mechanism of ROS, tumor targeting, and MDR reversal ability based on P-gp inhibition, which significantly inhibited the tumor growth of MCF-7/ADR tumor-bearing nude mice.

3 OTHER-RESPONSIVE DRUG DELIVERY SYSTEM BASED ON TPGS

Enzyme plays an important role in many biochemical processes, by triggering or catalyzing the physiological reaction. The expression of enzyme will change with concentration in different organization, which even specifically occurs in specific tissue. Since matrix metalloproteinases (MMPs) were highly expressed in various malignancies, oligopeptide GPVGLIGK-NH_2 (GK8) was inserted between α-tocopherol succinate (α-TOS) and polyethylene glycol monomethyl ether 2000 (mPEG2K) instead of succinate to form a TPGS analogue (TGK)[73]. Then, TGK was mixed with TPGS in a ratio of 40:60 to form hybrid micelles. In the presence of collagenase IV (a mixture of MMP-2 and MMP-9), PTX loaded in TGK micelles was effectively released, and the uptake

of micelles by HT1080 cells was doubled due to the breaking of GK8 under the MMP-2/9 environment compared to nonsensitive micelles mPEG2K-α-TOS. The hybrid micelles demonstrated good targeting and accumulation capacity, as well as strongest anti-tumor efficacy in HT1080 tumors model with minimal systemic toxicity.

The temperature is higher in some nidus such as cancer and inflammation than in normal tissue, which makes it possible to design a temperature-responsive nano-drug delivery system. Temperature-responsive delivery system based on TPGS is also one of the concerns. Zhao *et al*[74] successfully prepared mixed micelles based on TPGS and poly (N-isopropylacrylamide-co-N, N-dimethylacrylamide) 118-poly (D, L-lacticco-glycolic acid) 71 (PID118-b-PLA71), and modified with anti-GD2 antibody. The shell of the mixed micelle was thermo-responsive. When temperature is higher than the volume phase transition temperature (VPTT), the outer shell of the mixed micelles changes from hydrophilic to hydrophobic, and the particle size increases from 150 nm to 500 nm, leading to more drug release and enhanced cell endocytosis in neuroblastoma (NB) cells, as well as good activity against NB *in vitro*. F127 is a good thermo-responsive pharmaceutical excipient. Docetaxel nanocrystals (DOC-NCS) was added into TPGS-modified Pluronic F127 thermosensitive hydrosol to obtain injectable DOC-NCS-TPGS-PF127 hydrogel. The preparation was liquid at room temperature and could be injected locally. When injected into the body, it was converted into gel and conducive to continuous and stable release of the drug for 72 h since its gel point is between 30 and 35°C. The growth inhibition of DOC-NCS-TPGS-PF127 hydrogel on SMMC-7721/RT cells was significantly higher than that of DOC solution or PF127 gel containing DOC-NCS. This system could form a drug depot with P-gp inhibition capability and thus demonstrated a good therapeutic effect against drug-resistant solid tumors[75].

4 MULTI-RESPONSIVE DRUG DELIVERY SYSTEM BASED ON TPGS

In recent years, researchers have been trying to integrate a variety of different stimuli response functions into the drug delivery system to realize the smarter, more advanced and more precise controlled release of drug[76–80]. At present, the TPGS-based drug delivery system has been designed as dual responsive to different stimuli.

We constructed an intelligent nanocarrier with pH and redox dual response by linking PBAE and TPGS *via* disulfide bonds[81]. The carrier was prepared by Michael-type step polymerization using TPGS succinic cystamide macromonomer. The copolymer C32-g-TPGS could be self-assembled into NPs and used to encapsulate paclitaxel (PTX). When the drug-loaded NPs in acidic (pH=5.5) and reductive (DTT=10 mmol/L) environment, a burst release of PTX occurred due to the protonation of the C32 backbone and the disulfide bond breaking, while TPGS dissociated from the copolymer inhibited the efflux of P-gp on PTX to maintain the intracellular concentration of PTX at a high level, and greatly enhanced the cytotoxicity against drug-resistant cells (A2780/T) compared to Taxol (fig. 4). We also induced F127-FA into such system as the active targeting moiety to form hybrid micelles and to increase its tumor accumulation. This hybrid micelle increased the cell uptake, heightened toxicity to tumor

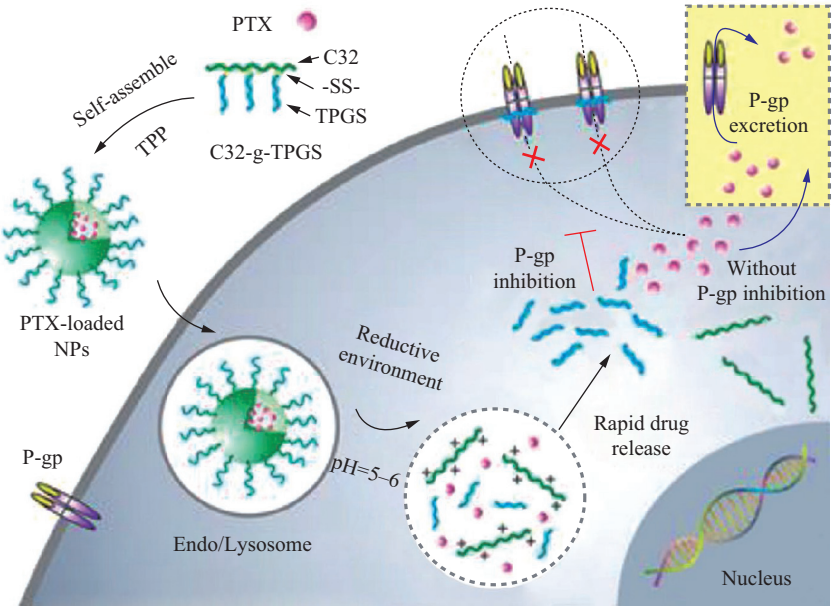

Fig. 4 Schematic illustration of pH-, redox dual-responsive C32-g-TPGS copolymers NPs for drug-controlled release and inhibition of MDR in tumor cells. Copyright 2020 from Elsevier[81]

cells, inhibited drug efflux, and exhibited a good effect to suppress the growth of drug-resistant tumor[82].

Multiple response would happen at the same time or step by step. Han *et al*[83] prepared the liposome-modified mesoporous silica NPs (LTMSNs) with dual response to pH and reduction for the DOX delivery. TPGS was attached to the surface of MSN by disulfide bond to obtain the lipid-coated layer by self-assembling. LTMSNs showed well pH and reductive dual response DOX release behavior, which was mainly affected by the dissociation of lipid layer and the electrostatic force between MSNs and DOX. Under the reductive condition in tumor cells, lipid layer was detached from the surface of the carrier because of the disulfide bond rupture, and the drug was diffused from the pores of NPs. On the other side, the DOX molecules were tightly entangled and rarely released due to the electrostatic interaction at pH7.4. When pH dropped to 5.0, the protonation effect of the silanol groups weakened the electrostatic force, which caused the release of DOX to increase again. Along with the effect of TPGS on inhibiting drug efflux and inducing tumor cell apoptosis, LTMSNs showed better uptake efficiency, greater cytotoxicity and higher intracellular accumulation in drug-resistant MCF-7/ADR cells.

Combining external stimuli with internal response could better regulate the drug release behavior of NPs. Sha *et al*[84] connected the photothermal conversion agent cypate to the surface of MSN by disulfide bond. DOX was encapsulated and coated with TPGS to construct the drug delivery system TCMSN. When the DOX-loaded TCMSN was taken up by tumor cells, cypate and TPGS detached from the surface of MSN due to the disulfide bond rupture. Cypate generated heat under NIR light to promote the release of DOX and lysosome escape, and realize thermotherapy. Before reaching the tumor cells, TPGS could improve the stability of the system and slow down the early release of drugs. In tumor cells, TPGS dissociated from the NPs to reduce the drug efflux and reverse multi-drug resistance. This kind of drug carrier with dual responsive release to GSH reduction and NIR photothermy combined the effect of hyperthermia with MDR inhibition, which presented enhanced anti-tumor activity compared with single treatment strategy.

5 CONCLUSION

The MDR seriously restricts the efficacy and application of chemotherapeutic drugs in tumor therapy, and TPGS exhibits various advantages including P-gp inhibition, good biological safety, mitochondria functional disruption, which make it become a prominent “star” in the field of reversing P-gp mediated tumor MDR. The development of environmental stimuli-responsive drug carriers is a promising direction for improving the efficiency of drug treatment, increasing the precision of drug release in tumor, and reducing the toxicity and side effects of chemotherapeutic drugs on normal tissues. At present, TPGS-based drug carriers with common stimuli-response including pH-response, redox-response, temperature response, and enzyme response, are effectively designed based on the specific characteristics of tumor microenvironment. In the past few years, more and more researchers focused on multiple response drug delivery systems, which can respond to two or more external stimuli signals. These reactions occurred at the same time or sequentially in the pathological site[85], so the drug can be more accurately delivered and released on lesion location and the anti-cancer efficacy can be further improved. However, most of the currently reported TPGS-based stimuli-responsive nanomedicine systems stay in the basic research stage, and there are still many problems to be solved in clinical development. In future, it is necessary to design more sophisticated and intelligent drug carriers combined with the TPGS, and to develop more convenient and responsive nano-drugs to achieve clinical translation.

Conflict of Interest Statement

The authors declare that they have no competing interest.

REFERENCES

1 Tan SW, Zou CM, Zhang W, *et al*. Recent developments in d-α-tocopheryl polyethylene glycol-succinate-based nanomedicine for cancer therapy. Drug Deliv, 2017, 24(1):1831-1842
2 Yang CL, Wu TT, Qi Y, *et al*. Recent advances in the application of vitamin E TPGS for drug delivery. Theranostics, 2018,8(2):464
3 Duhem N, Danhier F, Preat V. Vitamin E-based nanomedicines for anti-cancer drug delivery. J Control Release, 2014,182:33-44
4 Guo YY, Luo J, Tan SW, *et al*. The applications of Vitamin E TPGS in drug delivery. Eur J Pharm Sci, 2013,49(2):175-186
5 Zhang ZP, Tan SW, Feng SS. Vitamin E TPGS as a molecular biomaterial for drug delivery. Biomaterials, 2012,33(19):4889-4906
6 Zheng NN, Wu LH, Tang JL. Advance in Application of d-alpha-tocopherol polyethyleneglycol succinate in the field of pharmaceutics. Zhongguo Yaoxue Zazhi (Chinese), 2014,49(16):1373-1376
7 Dintaman JM, Silverman JA. Inhibition of P-glycoprotein by D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS). Pharm Res, 1999,16(10):1550-1556
8 Su RN, Liu TF, Zhu XM, *et al*. Application of TPGS-based nano-drug delivery system in reversing P-gp mediated multidrug resistance. Yaoxue Xuebao (Chinese), 2018,53(11):1797-1807
9 Liu TF, Liu XY, Xiong H, *et al*. Mechanisms of TPGS and its derivatives inhibiting P-glycoprotein efflux pump and application for reversing multidrug

resistance in hepatocellular carcinoma. Polym Chem, 2018,9(14):1827-1839
10 Collnot EM, Baldes C, Wempe MF, *et al*. Mechanism of inhibition of P-glycoprotein mediated efflux by vitamin E TPGS: influence on ATPase activity and membrane fluidity. Mol Pharm, 2007,4(3):465-474
11 Collnot EM, Baldes C, Schaefer UF, *et al*. Vitamin E TPGS P-glycoprotein inhibition mechanism: influence on conformational flexibility, intracellular ATP levels, and role of time and site of access. Mol Pharm, 2010,7(3):642-651
12 Hao TN, Chen DW, Liu KX, *et al*. Micelles of d-α-tocopheryl polyethylene glycol 2000 succinate (TPGS 2K) for doxorubicin delivery with reversal of multidrug resistance. ACS Appl Mater Interfaces, 2015,7(32): 18064-18075
13 Yu PC, Yu HJ, Guo CY, *et al*. Reversal of doxorubicin resistance in breast cancer by mitochondria-targeted pH-responsive micelles. Acta Biomater, 2015,14:115-124
14 Tuguntaev RG, Chen SZ, Eltahan AS, *et al*. P-gp inhibition and mitochondrial impairment by dual-functional nanostructure based on vitamin E derivatives to overcome multidrug resistance. ACS Appl Mater Interfaces, 2017,9(20):16900-16912
15 Wang DF, Rong WT, Lu Y, *et al*. TPGS2k/PLGA nanoparticles for overcoming multidrug resistance by interfering mitochondria of human alveolar adenocarcinoma cells. ACS Appl Mater Interfaces, 2015,7(7): 3888-3901
16 Wang AT, Liang DS, Liu YJ, *et al*. Roles of ligand and TPGS of micelles in regulating internalization, penetration and accumulation against sensitive or resistant tumor and therapy for multidrug resistant tumors. Biomaterials, 2015,53:160-172
17 Cabral H, Miyata K, Osada K, *et al*. Block copolymer micelles in nanomedicine applications. Chem Rev, 2018,118(14):6844-6892
18 Fenton OS, Olafson KN, Pillai PS, *et al*. Advances in biomaterials for drug delivery. Adv Mater, 2018,30(29): 1705328
19 Cagel M, Tesan FC, Bernabeu E, *et al*. Polymeric mixed micelles as nanomedicines: Achievements and perspectives. Eur J Pharm Biopharm, 2017,113:211-228
20 Lombardo D, Kiselev MA, Caccamo MT. Smart nanoparticles for drug delivery application: development of versatile nanocarrier platforms in biotechnology and nanomedicine. J Nanomater, 2019,1-26
21 Lu Y, Aimetti AA, Langer R, *et al*. Bioresponsive materials. Nat Rev Mater, 2016,2(1):1-17
22 Feng AC, Yuan JY. Smart nanocontainers: Progress on novel stimuli-responsive polymer vesicles. Macromol Rapid Commun, 2014,35(8):767-779
23 Zhang WM, Zhang J, Qiao Z, *et al*. Functionally oriented tumor microenvironment responsive polymeric nanoassembly: Engineering and applications. Chin J Polym Sci, 2018,36(3):273-287
24 Lu CL, Urban MW. Stimuli-responsive polymer nanoscience: Shape anisotropy, responsiveness, applications. Prog Polym Sci, 2018,78:24-46
25 Zhang XY, Han L, Liu MY, *et al*. Recent progress and advances in redox-responsive polymers as controlled delivery nanoplatforms. Mater Chem Front, 2017,1(5): 807-822
26 Stubbs M, McSheehy PMJ, Griffiths JR, *et al*. Causes and consequences of tumour acidity and implications for treatment. Mol Med Today, 2000,6(1):15-19
27 Engin K, Leeper DB, Cater JR, *et al*. Extracellular pH distribution in human tumours. Int J Hyperthermia, 1995,11(2):211-216
28 Van SR, Bhujwalla ZM, Raghunand N, *et al*. *In vivo* imaging of extracellular pH using 1H MRSI. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine, 1999,41(4):743-750
29 Murphy RF, Powers S, Cantor CR. Endosome pH measured in single cells by dual fluorescence flow cytometry: rapid acidification of insulin to pH 6. J Cell Biol, 1984,98(5):1757-1762
30 Schmid S, Fuchs R, Kielian M, *et al*. Acidification of endosome subpopulations in wild-type Chinese hamster ovary cells and temperature-sensitive acidification-defective mutants. J Cell Biol, 1989,108(4):1291-1300
31 Zhou MX, Zhang XC, Xie J, *et al*. pH-sensitive poly (β-amino ester) s nanocarriers facilitate the inhibition of drug resistance in breast cancer cells. Nanomaterials, 2018,8(11):952
32 Hung CC, Huang WC, Lin YW, *et al*. Active tumor permeation and uptake of surface charge-switchable theranostic nanoparticles for imaging-guided photothermal/chemo combinatorial therapy: erratum. Theranostics, 2017,7(3):559
33 Wang Q, Zou CM, Wang LY, *et al*. Doxorubicin and adjudin co-loaded pH-sensitive nanoparticles for the treatment of drug-resistant cancer. Acta Biomater, 2019, 94:469-481
34 Helmlinger G, Sckell A, Dellian M, *et al*. Acid production in glycolysis-impaired tumors provides new insights into tumor metabolism. Clin Cancer Res, 2002,8(4):1284-1291
35 Mi Y, Zhao J, Feng SS. Vitamin E TPGS prodrug micelles for hydrophilic drug delivery with neuroprotective effects. Int J Pharm, 2012,438(1-2):98-106
36 Khare V, Sakarchi WA, Gupta Prem N, *et al*. Correction: Synthesis and characterization of TPGS–gemcitabine prodrug micelles for pancreatic cancer therapy. RSC Advances, 2017,7(21):12598-12598
37 Gao YH, Ping QN, Zong L. Preparation and antitumor activity of mitoxantrone conjugated D-α-tocopherylpolyethylene glycol 1000 succinate prodrug micelle. Zhongguo Yaoke Daxue Xuebao (Chinese), 2016,47(03):311-316
38 Bao YL, Yin MX, Hu XM, *et al*. A safe, simple and efficient doxorubicin prodrug hybrid micelle for overcoming tumor multidrug resistance and targeting delivery. J Control Release, 2016,235:182-194
39 Hou WX, Zhao X, Qian XQ, *et al*. pH-Sensitive self-assembling nanoparticles for tumor near-infrared fluorescence imaging and chemo–photodynamic combination therapy. Nanoscale, 2016,8(1):104-116
40 Dong K, Lei QY, Qi HF, *et al*. Amplification of oxidative stress in MCF-7 cells by a novel pH-responsive amphiphilic micellar system enhances anticancer therapy. Mol Pharm, 2019,16(2):689-700

41 Lynn DM, Langer R. Degradable poly (β-amino esters): synthesis, characterization, and self-assembly with plasmid DNA. J Am Chem Soc, 2000,122(44):10761-10768
42 Ko JY, Park KS, Kim YS, *et al*. Tumoral acidic extracellular pH targeting of pH-responsive MPEG-poly (β-amino ester) block copolymer micelles for cancer therapy. J Control Release, 2007,123(2):109-115
43 Min KH, Kim JH, Bae SM, *et al*. Tumoral acidic pH-responsive MPEG-poly (β-amino ester) polymeric micelles for cancer targeting therapy. J Control Release, 2010,144(2):259-266
44 Chen YC, Bathula SR, Li J, *et al*. Multifunctional nanoparticles delivering small interfering RNA and doxorubicin overcome drug resistance in cancer. J Biol Chem, 2010,285(29):22639-22650
45 Zhao S, Tan SW, Guo YY, *et al*. pH-sensitive docetaxel-loaded d-α-tocopheryl polyethylene glycol succinate–poly (β-amino ester) copolymer nanoparticles for overcoming multidrug resistance. Biomacromolecules, 2013,14(8):2636-2646
46 Zhang JM, Li JJ, Shi Z, *et al*. pH-sensitive polymeric nanoparticles for co-delivery of doxorubicin and curcumin to treat cancer via enhanced pro-apoptotic and anti-angiogenic activities. Acta Biomater, 2017,58:349-364
47 Li Z, Qiu LP, Chen Q, *et al*. pH-sensitive nanoparticles of poly (L-histidine)-poly (lactide-co-glycolide)-tocopheryl polyethylene glycol succinate for anti-tumor drug delivery. Acta Biomater, 2015,11:137-150
48 Hu M, Chen JY, Li ZY, *et al*. Gold nanostructures: engineering their plasmonic properties for biomedical applications. Chem Soc Rev, 2006,35(11):1084-1094
49 Xing RR, Liu K, Jiao TF, *et al*. An injectable self-assembling collagen-gold hybrid hydrogel for combinatorial antitumor photothermal/photodynamic therapy. Adv Mater, 2016,28(19):3669-3676
50 Kankala RK, Liu CG, Chen AZ, *et al*. Overcoming multidrug resistance through the synergistic effects of hierarchical pH-sensitive, ROS-generating nanoreactors. ACS Biomater Sci Eng, 2017,3(10):2431-2442
51 Cheng W, Liang CY, Xu L, *et al*. TPGS-functionalized polydopamine-modified mesoporous silica as drug nanocarriers for enhanced lung cancer chemotherapy against multidrug resistance. Small, 2017,13(29)
52 Guissi NEI, Li HP, Xu YR, *et al*. Mitoxantrone-and folate-TPGS2K conjugate hybrid micellar aggregates to circumvent toxicity and enhance efficiency for breast cancer therapy. Mol Pharm, 2017,14(4):1082-1094
53 Zhang JL, Zhao XF, Chen Q, *et al*. Systematic evaluation of multifunctional paclitaxel-loaded polymeric mixed micelles as a potential anticancer remedy to overcome multidrug resistance. Acta Biomater, 2017,50:381-395
54 Kuppusamy P, Li HQ, Ilangovan G, *et al*. Noninvasive imaging of tumor redox status and its modification by tissue glutathione levels. Cancer Res, 2002,62(1):307-312
55 Deng B, Ma P, Xie Y. Reduction-sensitive polymeric nanocarriers in cancer therapy: a comprehensive review. Nanoscale, 2015,7(30):12773-12795
56 Rastew E, Vicente JB, Singh U. Oxidative stress resistance genes contribute to the pathogenic potential of the anaerobic protozoan parasite, Entamoeba histolytica. Int J Parasit, 2012,42(11):1007-1015
57 Rahman I. Oxidative stress, chromatin remodeling and gene transcription in inflammation and chronic lung diseases. J Biochem Mol Biol, 2003,36(1):95-109
58 Vaccari L, Canton D, Zaffaroni N, *et al*. Porous silicon as drug carrier for controlled delivery of doxorubicin anticancer agent. Microelectron Eng, 2006,83(4-9):1598-1601
59 Wei H, Zhuo RX, Zhang XZ. Design and development of polymeric micelles with cleavable links for intracellular drug delivery. Prog Polym Sci, 2013,38(3-4):503-535
60 Lee MH, Yang ZG, Lim CW, *et al*. Disulfide-cleavage-triggered chemosensors and their biological applications. Chem Rev, 2013,113(7):5071-5109
61 Brülisauer L, Gauthier MA, Leroux JC. Disulfide-containing parenteral delivery systems and their redox-biological fate. J Control Release, 2014,195:147-154
62 Bao YL, Guo YY, Zhuang XT, *et al*. D-α-tocopherol polyethylene glycol succinate-based redox-sensitive paclitaxel prodrug for overcoming multidrug resistance in cancer cells. Mol Pharm, 2014,11(9):3196-3209
63 Qiao HZ, Zhu ZZ, Fang D, *et al*. Redox-triggered mitoxantrone prodrug micelles for overcoming multidrug-resistant breast cancer. J Drug Target, 2018,26(1):75-85
64 Banala VT, Urandur S, Sharma S, *et al*. Targeted co-delivery of the aldose reductase inhibitor epalrestat and chemotherapeutic doxorubicin via a redox-sensitive prodrug approach promotes synergistic tumor suppression. Biomater Sci, 2019,7(7):2889-2906
65 Dong K, Yan Y, Wang PC, *et al*. Biodegradable mixed MPEG-SS-2SA/TPGS micelles for triggered intracellular release of paclitaxel and reversing multidrug resistance. Int J Nanomed, 2016,11:5109
66 Guo YY, Niu BN, Song QL, *et al*. RGD-decorated redox-responsive d-α-tocopherol polyethylene glycol succinate–poly (lactide) nanoparticles for targeted drug delivery. J Mat Chem B, 2016,4(13):2338-2350
67 Wang L, Xie X, Liu D, *et al*. iRGD-mediated reduction-responsive DSPE–PEG/LA–PLGA–TPGS mixed micelles used in the targeted delivery and triggered release of docetaxel in cancer. RSC Adv, 2016,6(34):28331-28342
68 Song QL, Tan SW, Zhuang XT, *et al*. Nitric oxide releasing D-α-tocopheryl polyethylene glycol succinate for enhancing antitumor activity of doxorubicin. Mol Pharm, 2014,11(11):4118-4129
69 Yin MX, Tan SW, Bao YL, *et al*. Enhanced tumor therapy via drug co-delivery and in situ vascular-promoting strategy. J Control Release, 2017,258:108-120
70 Qi Y, Qin XY, Yang CL, *et al*. Micelle system based on molecular economy principle for overcoming multidrug resistance and inhibiting metastasis. Mol Pharm, 2018,15(3):1005-1016
71 Xu CF, Sun Y, Qi Y, *et al*. Selective self-induced stimulus amplification prodrug platform for inhibiting multidrug resistance and lung metastasis. J Control Release, 2018,284:224-239
72 Su ZG, Chen ML, Xiao YY, *et al*. ROS-triggered and regenerating anticancer nanosystem: An effective strategy to subdue tumor's multidrug resistance. J

Control Release, 2014,196:370-383
73 Zhang XY, Wang XF, Zhong WT, *et al*. Matrix metalloproteinases-2/9-sensitive peptide-conjugated polymer micelles for site-specific release of drugs and enhancing tumor accumulation: preparation and in vitro and *in vivo* evaluation. Int J Nanomed, 2016,11:1643
74 Zhao H, Jing MF, Li ZH, *et al*. Potentiating chemotherapy efficacy in neuroblastoma cells via disialoganglioside2 targeting mixed micelles. J Nanosci Nanotechnol, 2016,16(12):12307-12315
75 Gao L, Wang XQ, Ma JL, *et al*. Evaluation of TPGS-modified thermo-sensitive Pluronic PF127 hydrogel as a potential carrier to reverse the resistance of P-gp-overexpressing SMMC-7721 cell lines. Colloid Surf B: Biointerfaces, 2016,140:307-316
76 Rapoport N. Physical stimuli-responsive polymeric micelles for anti-cancer drug delivery. Prog Polym Sci, 2007,32(8-9):962-990
77 Zhang QS, Zha LS, Ma JH, *et al*. A novel route to prepare pH-and temperature-sensitive nanogels via a semibatch process. J Colloid Interface Sci, 2009,330(2):330-336
78 Guo M, Yan Y, Zhang HK, *et al*. Magnetic and pH-responsive nanocarriers with multilayer core–shell architecture for anticancer drug delivery. J Mater Chem, 2008,18(42):5104-5112
79 Feng HK, Zhao Y, Pelletier M, *et al*. Synthesis of photo- and pH-responsive composite nanoparticles using a two-step controlled radical polymerization method. Polymer, 2009,50(15):3470-3477
80 Isojima T, Lattuada M, Vander SJB, *et al*. Reversible clustering of pH-and temperature-responsive Janus magnetic nanoparticles. Acs Nano, 2008,2(9):1799-1806
81 Bao YL, Kong M, Gao XQ, *et al*. pH-, redox dual-sensitive poly (β-amino ester)-g-TPGS copolymer nanoparticles for drug delivery and inhibition of multidrug resistance in cancer. React Funct Polym, 2017,120:131-138
82 Yin MX, Bao YL, Gao XQ, *et al*. Redox/pH dual-sensitive hybrid micelles for targeting delivery and overcoming multidrug resistance of cancer. J Mat Chem B, 2017,5(16):2964-2978
83 Han N, Zhao QF, Wan L, *et al*. Hybrid lipid-capped mesoporous silica for stimuli-responsive drug release and overcoming multidrug resistance. ACS Appl Mater Interfaces, 2015,7(5):3342-3351
84 Sha LP, Zhao QF, Wang D, *et al*. "Gate" engineered mesoporous silica nanoparticles for a double inhibition of drug efflux and particle exocytosis to enhance antitumor activity. J Colloid Interface Sci, 2019,535:380-391
85 Cheng R, Meng FH, Deng C, *et al*. Dual and multi-stimuli responsive polymeric nanoparticles for programmed site-specific drug delivery. Biomaterials, 2013, 34(14):3647-3657

(Received Jan. 10, 2020; revised Mar. 7, 2020)