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EXPERT OPINION

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Reduction-sensitive degradable micellar nanoparticles as smart and intuitive delivery systems for cancer chemotherapy

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Introduction: Biodegradable micellar nanoparticles are one of the most promising platforms for targeted cancer chemotherapy. In particular, reduction-sensitive micellar nanoparticles that actively deliver and release drugs into cancer cells have recently appeared as an advanced drug release system. The *in vitro* and *in vivo* studies have pointed out that reduction-sensitive micellar drug formulations afford significantly enhanced antitumor activity as compared with 'traditional' reduction-insensitive counterparts.
Areas covered: This review provides an overview of recent advances in reduction-sensitive degradable micellar nanoparticles for triggered anticancer drug delivery. The design and preparation of reduction-sensitive micellar nanoparticles, redox-triggered *in vitro* and intracellular drug release, *in vitro* as well as *in vivo* antitumor performances of drug-loaded nanoparticles are discussed.
Expert opinion: Reduction-sensitive degradable micellar nanoparticles with unique advantages of high stability against hydrolytic degradation, fast response to intracellular reducing environment and triggered drug release right in the cytosol and cell nucleus have demonstrated a tremendous potential in targeted and active intracellular delivery of potent and poorly soluble anticancer drugs. These intracellular-activatable fast drug releasing nanosystems may eventually be developed as 'drug bomb' for effective treatment of various tumors including multidrug-resistant tumors.

Keywords: anticancer drugs, cancer therapy, degradable micelles, disulfide-crosslinking, intracellular drug release, nanoparticles, reduction-sensitive, tumor-targeting

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1. Introduction

In the past decades, biodegradable micellar nanoparticles self-assembled from amphiphilic copolymers have attracted widespread interest for tumor-targeting delivery of potent and poorly soluble anticancer drugs [1-5]. It is interesting to note that several biodegradable micellar anticancer drugs (e.g., NK911 [6], NK105 [7], NK012 [8] and NC6004 [9]) have advanced to different phases of clinical trials [3,10]. Genexol-PM, a micellar paclitaxel (PTX) formulation, has been approved for the treatment of breast, lung and ovarian cancers in South Korea [11]. These micellar drug formulations hold significant advantages, such as prolonged circulation time, decreased adverse effects, improved drug availability and better pharmacological profiles over the conventional clinical approaches.

It should be noted, however, that current micellar nanoparticles often expose slow and deficient drug release at the pathological site, leading to compromised therapeutic effects [12,13]. To this end, tremendous efforts have been directed to the

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Article highlights.

- This review introduces unique features of reduction-sensitive degradable micellar nanoparticles.
- This review overviews recent advances in reduction-sensitive degradable micellar nanoparticles for triggered intracellular anticancer drug release.
- This review provides a comprehensive list of reduction-sensitive micellar nanoparticles developed for active drug release.
- This review highlights reduction-sensitive reversible crosslinking approach to elegantly resolve the stability and drug release dilemma of nanoparticulate drug delivery systems.
- This review gives personal opinions on future development of reduction-sensitive micellar drug formulations.

This box summarizes key points contained in the article.

development of smart bio-responsive nanocarriers that are sufficiently stable under extracellular conditions while release drugs rapidly and efficiently in cancer cells. For example, taking advantages of the acidic environments in the endo/lysosomal compartments and highly reducing conditions in the cytosol and cell nucleus, various pH-sensitive and reduction-sensitive nanoparticles have been designed and developed [14-17]. In recent years, reduction-sensitive degradable micellar nanoparticles have received particular attention [18-20], in that: i) they exhibit extremely fast response, at a time scale from minutes to hours, to the intracellular reducing environment; ii) they are intended to disassemble and release drugs in the cytosol and cell nucleus where exactly many anticancer drugs take action and iii) they are rather stable under extracellular conditions and during workup. The high reducing potential in the cytosol and cell nucleus is mainly due to presence of 2 – 10 mM glutathione tripeptide (γ-glutamyl-cysteinyl-glycine, GSH) which is the most abundant low molecular weight biological reducing agent and is kept reduced by NADPH and glutathione reductase [21]. By contrast, body fluids and normal extracellular matrices contain only about 2 – 20 μM GSH. Notably, high reducing potential has also been observed in the endosomal compartment where redox potential is modulated by γ-interferon-inducible lysosomal thiol reductase (GILT) in the copresence of reducing agents other than GSH such as cysteine. Moreover, tumor tissues contain at least four times higher concentration of GSH than normal tissues [22]. Therefore, reduction is a ubiquitous and unique biological stimulus that is able to trigger drug release in both cancer cells and tumor tissues.

This review provides an overview of recent advances in reduction-sensitive degradable micellar nanoparticles for triggered anticancer drug delivery. Here, micellar nanoparticles refer to core-shell structured micelles as well as water-dispersible micelle-like nano-assemblies. Interestingly, reduction-sensitive micellar nanoparticles have been prepared from varying amphiphilic copolymers including linear, star, hyperbranched and graft copolymers and investigated for controlled delivery of different drugs such as PTX, doxorubicin (DOX) and camptothecin (CPT) (**Table 1**). Furthermore, reversibly crosslinked micellar nanoparticles that simultaneously meet the conflicting requirements of high extracellular stability and fast intracellular drug release have been designed and developed through versatile disulfide crosslinking (**Table 2**).

2. Reduction-sensitive micellar nanoparticles based on varying amphiphilic copolymers

2.1 Reduction-sensitive micellar nanoparticles based on amphiphilic linear block copolymers

Reduction-sensitive degradable micellar nanoparticles have been obtained from various amphiphilic linear block copolymers that contain an intervening disulfide bond between the hydrophobic and hydrophilic blocks. The cleavage of disulfide bond in response to a reducing environment results in shedding of hydrophilic shells from micelles. These micelles are, therefore, termed as shell-sheddable micelles. For example, Sun *et al.* developed reduction-sensitive shell-sheddable micelles based on biodegradable poly(ethylene glycol)-SS-poly(ε-caprolactone) (PEG-SS-PCL) and dextran-SS-PCL (Dex-SS-PCL) diblock copolymers (**Figure 1A**) [23,24]. These shell-sheddable micelles while showing sufficient stability in phosphate buffer (PB) (50 mM, 7.4), rapidly formed large aggregates in response to 10 mM dithiothreitol (DTT). Interestingly, *in vitro* release studies showed that DOX was quantitatively released from shell-sheddable micelles within 12 h under a reductive environment analogous to that of the intracellular compartments such as cytosol and the cell nucleus, whereas low drug release (< 30%) was observed for the reduction-insensitive micelles under the same conditions as well as for reduction-sensitive micelles under a non-reductive environment. The confocal microscopy observations revealed that these shell-sheddable micelles accomplished fast intracellular DOX release in mouse leukemic monocyte macrophage cell line (RAW 264.7). MTT assays demonstrated that DOX-loaded Dex-SS-PCL micelles induced significantly enhanced antitumor effects as compared with the reduction-insensitive Dex-PCL control (cell viabilities: about 20 vs 70%) (**Figure 1B**). More recently, Wang *et al.* found that the intracellular drug release and therefore antitumor activity of DOX-loaded PEG-PCL micelles was dependent on the extent of shell-shedding [25]. Tang *et al.* reported that shell-detachable biodegradable micelles self-assembled from poly(ethyl ethylene phosphate)-SS-PCL (PEEP-SS-PCL) diblock copolymer displayed intracellular GSH-dependent DOX release behavior [26]. The results showed that antitumor activity of DOX-loaded PEEP-SS-PCL micelles was improved in A549 cells pretreated with glutathione monoester (GSH-OEt). GSH-OEt is often used to artificially enhance the

Table 1. Reduction-sensitive micellar nanoparticles based on amphiphilic copolymers for controlled drug delivery.

Polymer	Model drug	Refs.
Linear block copolymers		
PEG-SS-PCL	DOX	[23,25]
Dex-SS-PCL	DOX	[24]
PEEP-SS-PCL	DOX	[26,27]
PEG-SS-PLA	PTX	[28]
CPT-SS-PEG-SS-CPT	CPT	[29]
POEOMA-SS-PLA	-	[30]
PEG-SS-PLeu	DOX	[31]
PEG-SS-PZLL	DOX	[32]
PEG-SS-PBLG	CPT, DOX and SN-38	[33-35]
PEG-SS-PTMBPEC	DOX	[36]
PNIPAM-SS-P(THP-HEMA)	Nile red	[37]
PEO-b-PMABC	DOX	[38]
PEG-b-P(PEGMMA-co-MABC)	PTX	[39]
PEG-b-P(MAOHD-Py)	Py	[40]
PEG-b-PPS-SS-TG	TG	[41]
POEOMA-b-PAP-b-POEOMA	-	[42]
POEOMA-SSPES	Nile red	[43]
PEO-b-P(DS-alt-NB)-b-PEO	Nile red	[44]
PEG-b-PUSS$_x$-b-PEG	Pyrene	[45]
Poly(ether urethane)s	DOX	[46]
PEG-b-PUSeSe-b-PEG	Rhodamine B	[47]
Star and hyperbranched copolymers		
6sPCL-SS-PEG	DOX	[48]
SS-4sPDEGGlu	DOX	[49]
H40-star-PLA-SS-PEP	DOX	[50]
HPHSEP	DOX	[51]
HPHSEP-star-PEP	DOX	[52]
HPSe	HPSe and DOX	[53]
Graft copolymers		
SSPAA-g-PEG	DOX	[54]
SSPAA-g-PEG/CPT	CPT	[55]
SSPAE-g-PEG/PBA	DOX	[56]
SSPAE$_{TMDP}$-g-PEG	DOX	[57]
PAA-g-SS-cholesterol	Azobenzene and Estradiol	[58]
HA-g-SS-DOCA	PTX	[59]
PAAc-g-TEG/SSUD	DOX	[60]
PAAc-g-mPEG/SS-PTX	PTX	[61]
PAsp-g-SS-mPEG/6-MP	6-MP	[62]
Chitosan-g-SS-PCL	DOX	[63]
PPDSEA-g-PEG/cRGD	DOX	[64]
PCL-g-SS-PEG	DOX	[65]

CPT: Camptothecin; DOX: Doxorubicin; 6-MP: 6-Mercaptopurine; PTX: Paclitaxel; Py: Pyrenebutyric acid; TG: Tioguanine.

intracellular GSH level. Notably, DOX-loaded PEEP-SS-PCL micelles displayed enhanced drug accumulation and retention in DOX-resistant MCF-7 cells effectively overcoming multidrug resistance (MDR) [27].

The rapid intracellular drug release achieved by PEG-SS-PCL and PEEP-SS-PCL micelles has inspired development of various reduction-sensitive shell-sheddable block copolymer micellar nanoparticles. For example, rice-like shell-sheddable nanoparticles were prepared from PEG-SS-poly(lactic acid) (PEG-SS-PLA) by oil-in-water (O/W) emulsion/solvent evaporation method [28]. Cell experiments showed that PTX-loaded PEG-SS-PLA nanoparticles exhibited improved cellular uptake and higher cytotoxicity to A549, MCF-7 and HeLa cells as compared with free PTX. Reduction-sensitive shell-sheddable CPT prodrug micelles were obtained with a size of about 226 nm and a critical micelle concentration (CMC) of 60 μg/ml from CPT-SS-PEG-SS-CPT [29]. CPT-SS-PEG-SS-CPT micelles exhibited apparent biphasic release kinetics in the presence of 10 mM DTT, wherein release rate of 4.0 h^{-1} in the first 10 h while only 0.4 h^{-1} during the following 10 days was observed. Khorsand *et al.* developed reduction-sensitive shell-sheddable micelles from poly[oligo (ethylene glycol) monomethyl ether methacrylate]-SS-PLA (POEOMA-SS-PLA) diblock copolymer [30]. The shedding of POEOMA shells in the presence of equivalent DTT relative to disulfide groups caused aggregation of core-forming PLA. Ren *et al.* and Wen *et al.* reported that reduction-sensitive shell-sheddable polypeptide micelles based on PEG-SS-poly(ε-benzyloxycarbonyl-L-lysine) (PEG-SS-PZLL) or PEG-SS-poly(leucine) (PEG-SS-PLeu) diblock copolymer afforded accelerated DOX release in response to 10 mM GSH or DTT [31,32]. DOX-loaded PEG-SS-PZLL and PEG-SS-PLeu micelles displayed GSH-dependent cell inhibition effect to MCF-7 and HepG2 cells. Thambi *et al.* reported that reduction-sensitive PEG-SS-poly(γ-benzyl L-glutamate)s (PEG-SS-PBLG) micelles had high loading efficiency for CPT and DOX [33,34]. CPT or DOX-loaded PEG-SS-PBLG micelles provoked higher cytotoxicity to SCC7 cancer cells than reduction-insensitive PEG-PBLG controls. Similarly, PEG-SS-PBLG micelles loaded with 7-ethyl-10-hydroxy-camptothecin (SN-38) showed increased cytotoxicity to L929 mouse muscular cells as compared with SN-38-loaded reduction-insensitive PEG-PBLG micelles [35].

Recently, reduction and pH dual-sensitive shell-sheddable micelles were prepared from PEG-SS-poly(2,4,6-trimethoxybenzylidene-pentaerythritol carbonate) (PEG-SS-PTMBPEC) [36]. The release studies showed that DOX release was markedly enhanced at pH 5.0 or in the presence of 10 mM GSH at pH 7.4. The fastest DOX release was, however, observed at pH 5.0 and 10 mM GSH, in which about 94.2% DOX was released in 10 h. Interestingly, DOX was transported into the cell nuclei following 8 h incubation. DOX-loaded PEG-SS-PTMBPEC micelles exhibited high antitumor activity with IC_{50} (half maximal inhibitory concentration) of 0.75 and 0.60 μg DOX equiv./ml for HeLa and RAW 264.7 cells, respectively. Temperature, pH and redox triple-sensitive micelles were prepared from poly(*N*-isopropylacrylamide)-SS-poly(tetrahydropyran-protected 2-hydroxyethyl methacrylate) (PNIPAM-SS-P(THP-HEMA)) block copolymer [37]. The *in vitro* release studies showed that these triple-sensitive micelles provide a unique possibility to fine tune the release kinetics of the encapsulated hydrophobic guest molecules. For example, it has been shown that release of Nile red from PNIPAM-SS-P(THP-HEMA) micelles was rather slow at either pH 5.0 or 3.2 mM GSH (< 30% release in 24 h), whereas combination of both stimuli resulted in complete release of Nile red in 24 h.

Table 2. Reduction-sensitive disulfide-crosslinked micellar nanoparticles for controlled drug delivery.

Polymer	Crosslinker or catalyst	Model drug	Refs.
Core-crosslinking			
Dextran-g-lipoic acid	DTT	DOX	[67]
PEG-b-PHPMA-lipoic acid	DTT	DOX	[68]
PEO-b-P(NIPAM-co-NAS)	Cystamine	-	[69]
PAEMA-b-P(NIPAM-co-DSDMA)	DSDMA	-	[70]
PPEGMEMA-b-PMAU	DSDMA	Riboflavin	[71]
PHPMA-b-PPDSEMA-DOX	TCEP	DOX	[72]
PEG-b-P(MA-g-Hyd-DOX)	Dithiodiethanoic acid	DOX	[73]
PEO-b-PMA	Cystamine	DOX	[74]
PEG-b-PLys-PDS	DODT	Ova/CpG-DNA, catalase	[75]
PEG-b-Cys_4-Lys_8-CA_8	O_2	PTX	[76]
PEG-b-(LA-co-MTC_{SH})	O_2	DOX	[77]
Pluronic F127-g-SH	O_2	PTX	[78]
Pluronic F127-g-benzaldehyde and Pluronic F127-g-cystamine	-	Taxol	[79]
PEG-b- poly(Tyr(alkynyl)-OCA)	*Bis*-(Azidoethyl) disulfide	Nile red	[80]
PEG-b-PDBTCL-N_3	Propargyl 3,3′-dithiopropionate	-	[81]
PEO-b-P(CL-co-(α-N_3CL)), PEO-b-PCL-b-P(α-N_3CL)	BEPDS	-	[82]
Shell-crosslinking			
PEO-b-P(α-N_3CL)-b-PCL	BEPDS	-	[82]
PEG-b-PLys-b-PPhe	DTSSP	MTX and DTX	[83,84]
PDEAEMA-b-PSt	BAEDS	IND	[85]
PEG-b-PLG-b-$(PLA)_2$	Cystamine	DOX	[86]
Pluronic F127 and P123	Au nanoparticles	PTX	[87]
Surfactant with three alkynes	*Bis*(2-Azidoethyl)disulfide	Pyrene	[88]
PEG-L_2-PCL	DTT	DOX	[89]
PEG-Cys_3-PCL	O_2	DOX	[90]
PEG-Cys_4-PDLLA	O_2	DOX	[91]
PEG-b-PCys-b-PPhe	O_2	DOX	[92]
PEG-b-PPE_{SH}-b-PCL	H_2O_2	DOX	[93]
PEG-b-PAsp(MEA)-b-PAsp(DIP)	O_2	DOX	[94]
mPEO-b-PAPMA-b-PDPAEMA	DTBP	-	[95]

BAEDS: *Bis*(acryloyloxyethyl) disulfide; BEPDS: *Bis*(ethyl-4-pentynoate)disulfide; DOX: Doxorubicin; DSDMA: *Bis*(2-methacryloyloxyethyl) disulfide; DTBP: Dimethyl 3,3′-dithiobispropionimidate; DTSSP: 3,3′-Dithiobis(sulfosuccinimidylpropionate); DTT: Dithiothreitol; DTX: Docetaxel; IND: Indomethacin; MTX: Methotrexate; PTX: Paclitaxel; TCEP: Tri(2-carboxyethyl)phosphine.

In addition to shell-sheddable micellar nanoparticles that contain a single disulfide linkage between hydrophilic and hydrophobic blocks, reduction-sensitive degradable micellar nanoparticles have also been developed from amphiphilic block copolymers consisting of disulfide or diselenide bonds in the hydrophobic regime. For instance, Sun *et al.* developed reduction-sensitive degradable micelles based on poly(ethylene oxide)-b-poly(*N*-methacryloyl-*N*′-(t-butyloxycarbonyl) cystamine) (PEO-b-PMABC) diblock copolymers that possess disulfide bonds in the side chain of PMABC block [38]. DOX-loaded PEO-b-PMABC micelles showed much faster DOX release after treatment with 10 or 20 mM DTT due to increased hydrophilicity of micellar core. The cytotoxicity studies demonstrated that DOX-loaded PEO-b-PMABC micelles had higher antitumor efficacy than the reduction-insensitive controls. Jiang *et al.* reported that reduction and thermo dual-sensitive degradable micelles based on PEG-b-poly(PEG methyl methacrylate-co-MABC) PEG-b-P (PEGMMA-co-MABC) diblock copolymer accomplished rapid PTX release in the presence of 10 mM DTT and higher antitumor activity in HepG2 cells than free PTX [39]. Yuan *et al.* developed reduction-sensitive micelles from pyrenebutyric acid (Py) functionalized PEG-b-poly(2-(methacryloyl)oxyethyl-2′-hydroxyethyl disulfide) (PEG-b-P (MAOHD-Py)) diblock copolymer [40]. Py was released rapidly on addition of tributylphosphine. van der Vlies *et al.* prepared reduction-sensitive PEG-b-poly(propylene sulfide)-SS-tioguanine (PEG-b-PPS-SS-TG) prodrug micelles with average sizes ranging from 18 to 40 nm [41]. TG was released in response to cysteine. The released TG retained bioactivity and inhibited growth of OVA-B16-F10 melanoma cells in a dose-dependent manner. Khorsand *et al.* obtained reduction-responsive micelles based on POEOMA-b-poly[oligo(propylene oxide) monononylphenyl ether acrylate]-b-POEOMA (POEOMA-b-PAP-b-POEOMA) triblock copolymer containing a single disulfide linkage in the hydrophobic PAP block [42]. The micelles with an average size of about 110 nm degraded into smaller-sized assemblies (about 70 nm) in the presence of DTT. Reduction-sensitive micelles based on amphiphilic POEOMA-b-SSPES (SSPES: polyester with disulfide bonds on the main chain at regular intervals) diblock copolymer were reported to enable fast release of encapsulated Nile red

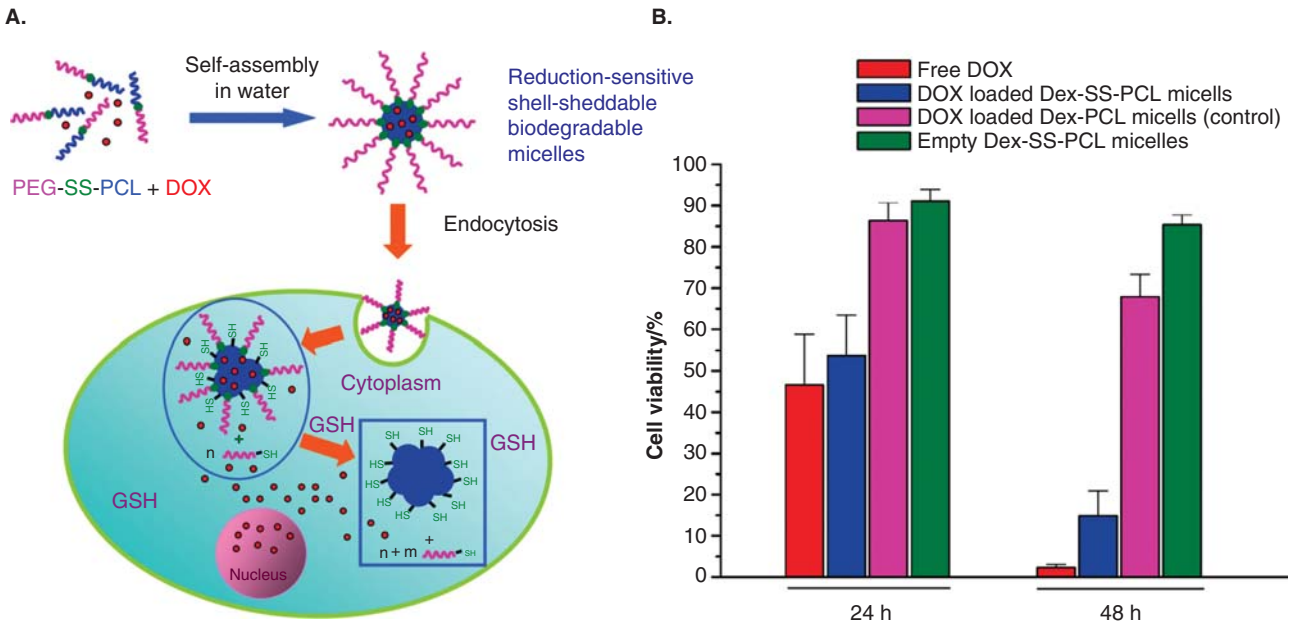

Figure 1. Reduction-sensitive shell-sheddable biodegradable micelles for triggered intracellular DOX release. A. Illustration of PEG-SS-PCL micelles for triggered intracellular release of DOX. **B.** Toxicity of DOX-loaded reduction-sensitive shell-sheddable Dex-SS-PCL micelles vs DOX-loaded reduction-insensitive Dex-PCL micelles, free DOX and empty Dex-SS-PCL micelles in RAW 264.7 cells (DOX dosage: 25 μg/ml).

A. Reproduced with permission from Elsevier [23]. **B.** Reproduced with permission from American Chemical Society [24].

in the presence of DTT due to reductive degradation of polyester main chain [43]. Reduction and light dual-sensitive micelles were prepared from PEO-b-poly(disulfide-alt-nitrobenzene)-b-PEO (PEO-b-P(DS-alt-NB)-b-PEO) triblock copolymer containing DS and NB groups alternatively in the main chain of hydrophobic P(DS-alt-NB) block [44]. These dual-sensitive micelles accomplished either burst release of Nile red by exposure to UV or slow release in response to DTT. The combination of both stimuli could achieve on-demand drug release profiles. Tong *et al.* prepared reduction-sensitive micelles from PEG-b-polyurethane-b-PEG (PEG-b-PUSS$_x$-b-PEG) triblock copolymers containing different amounts of disulfide bonds in the PU block [45]. The release studies demonstrated that release of pyrene in the presence of DTT increased with increasing disulfide contents. Thermo and reduction dual-sensitive micellar nanoparticles were developed from a series of multi-segmented amphiphilic poly(ether urethane)s consisting of 2,2′-dithiodiethanol, hexamethylene diisocyanate and PEG [46]. The fastest DOX release was obtained under high temperature (> lower critical solution temperature, LCST) in the presence of 10 mM GSH. The results showed that cytotoxicity of DOX-loaded nanoparticles against HepG2 cells was close to free DOX. Ma *et al.* developed novel redox-sensitive micelles based on diselenide containing PEG-b-PUSeSe-b-PEG triblock copolymer [47]. Notably, these micelles exhibited fast response to both reducing and oxidizing agents, in which Rhodamine B was rapidly released at 0.01 mg/ml GSH or 0.01% v/v H_2O_2.

2.2 Reduction-sensitive micellar nanoparticles based on amphiphilic star and hyperbranched copolymers

Shell-sheddable micelles have been prepared from hexa-arm star-shaped 6s-PCL-SS-PEG copolymers [48]. The resulting micelles though stable under a normal condition quickly aggregated and released DOX in response to 10 mM DTT. DOX-loaded 6s-PCL-SS-PEG micelles showed GSH-dependent cytotoxicity to MCF-7 cells. Very recently, Liu *et al.* obtained reduction and thermo dual-sensitive polypeptide micelles based on tetra-armed polypeptide SS-4s-PDEGGlu that was prepared via ring-opening polymerization of diethylene glycol-L-glutamate *N*-carboxyanhydride using disulfide-bond-cored tetra-amine as an initiator [49]. The size of micelles was reduced to half in response to 10 mM DTT in that SS-4s-PDEGGlu copolymer was cleaved into linear subunits with the same hydrophobic:hydrophilic ratio. The *in vitro* release studies showed that release of DOX from SS-4s-PDEGGlu micelles was not much enhanced by presence of 10 mM DTT.

Reduction-sensitive micelles have also been developed from disulfide or diselenide containing amphiphilic hyperbranched copolymers. For example, Liu *et al.* developed reduction-sensitive shell-sheddable micelles from amphiphilic hyperbranched multi-arm copolymer, H40-star-PLA-SS-poly (2-ethoxy-2-oxo-1,3,2-dioxaphospholane) (H40-star-PLA-SS-PEP) [50]. These micelles formed large aggregates rapidly in the presence of 10 mM DTT and exhibited faster intracellular DOX release as well as higher cellular proliferation

inhibition in GSH-OEt pretreated HeLa cells. Reduction-sensitive micelles were also constructed from amphiphilic hyperbranched homopolyphosphates (HPHSEP) that were prepared by self-condensing ring-opening polymerization of 2-[(2-hydroxyethyl)-disulfanyl] ethoxy-2-oxo-1,3,2-dioxaphospholane [51]. Confocal microscopy observations showed that HPHSEP micelles rapidly and efficiently transported DOX into the nuclei of HeLa cells pretreated with 10 mM GSH-OEt. DOX-loaded HPHSEP micelles exhibited enhanced cell inhibition against GSH-OEt pretreated HeLa cells, and reduced inhibition toward buthionine sulfoximine (BSO, an inhibitor for the intracellular synthesis of GSH) pretreated cells. In a following study, amphiphilic hyperbranched multi-arm copolyphosphates, HPHSEP-star-PEP, with a reduction-sensitive core were obtained by ring-opening polymerization of 2-ethoxy-2-oxo-1,3,2-dioxaphospholane using HPHSEP-OH as a macroinitiator [52]. HPHSEP-star-PEP formed micelles with an average size ranging from 70 to 100 nm, which were rapidly destructed in 10 mM DTT. The *in vitro* release of DOX was shown to be DTT-dependent. DOX was released into the nuclei of HeLa cells, resulting in enhanced antitumor efficacy. Multi-core/shell structured micelles were obtained from novel hyperbranched polydiselenide (HPSe) consisting of alternative hydrophobic diselenide bonds and hydrophilic phosphate moieties [53]. HPSe micelles exhibited fast response to reduction stimulus and rapidly released DOX into nuclei of HeLa cells.

2.3 Reduction-sensitive micellar nanoparticles based on amphiphilic graft copolymers

In addition to linear, star and hyperbranched copolymers, reduction-sensitive micellar nanoparticles have also been developed from graft copolymers containing disulfide bonds on the main chain or side chain. For instance, Sun *et al.* developed reduction-sensitive degradable micelles from amphiphilic poly(amide amine)-g-PEG (SSPAA-g-PEG) copolymer containing multiple disulfide bonds in the hydrophobic PAA main chain [54]. The micelles released DOX nearly quantitatively within 10 h in the presence of 1 mM DTT due to micelle disassembly. Cell experiments indicated that SSPAA-g-PEG micelles effectively transported DOX into the nuclei of both HeLa and HepG2 cells, resulting in high antitumor efficacy. Reduction-sensitive degradable CPT prodrug nanoparticles were prepared with an average size of about 88 nm from SSPAA-g-PEG/CPT conjugate [55]. SSPAA-g-PEG/CPT micelles showed enhanced *in vitro* release of CPT at higher DTT concentration. Chen *et al.* prepared reduction-sensitive micelles from poly(β-amino ester)-g-PEG/phenylbutylamine (SSPAE-g-PEG/PBA) graft copolymers containing disulfide bonds throughout the PAE main chain [56]. These micelles released about 80% of DOX within 6 h in response to 10 mM DTT, whereas only about 20% of DOX was released for reduction-insensitive control under otherwise the same conditions even after 24 h. DOX-loaded SSPAE-g-PEG/PBA micelles exhibited high antitumor efficacy in HepG2 cells with IC_{50} two times lower than free DOX. Notably, pH and reduction dual-sensitive micelles self-assembled from reduction-sensitive degradable amphiphilic $SSPAE_{TMDP}$-g-PEG graft copolymer prepared from 2,2′-dithiodiethanol diacrylate, 4,4′-trimethylene dipiperidine (TMDP) and mPEG-NH_2, accomplished accelerated DOX release at pH 6.5 or in the presence of 5 mM DTT at pH 7.4 [57]. Fast DOX release was further observed in response to both stimuli (pH 6.5 and 5 mM DTT). Cell experiments showed that these pH and reduction dual-sensitive micelles could effectively deliver DOX into the cell nuclei, with IC_{50} of DOX-loaded micelles close to free DOX in HepG2 cells.

Redox-sensitive nanoparticles with an average size ranging from 100 to 300 nm were prepared from PAA-g-SS-cholesterol conjugates [58]. These nanoparticles could encapsulate 9 – 20 wt.% of hydrophobic agents such as azobenzene and estradiol. Hyaluronic acid-SS-deoxycholic acid (HA-g-SS-DOCA) conjugates formed nano-sized micelles which rapidly disassembled in response to 20 mM GSH [59]. Notably, HA-SS-DOCA micelles were taken up by human breast adenocarcinoma cells (MDA-MB-231) via HA receptor-mediated endocytosis. *In vitro* cytotoxicity studies indicated that PTX-loaded HA-SS-DOCA micelles achieved significant higher antitumor activity with an IC_{50} of 25.6 ng/ml following 72 h treatment as compared with PTX-loaded HA-DOCA micelles (IC_{50} = 56.6 ng/ml) and taxol (IC_{50} = 51.7 ng/ml). The *in vivo* studies in tumor-bearing mice revealed preferential accumulation of payloads in the tumor site at 24 h following injection. Ryu *et al.* reported that micelles based on poly(acrylic acid)-g-(triethylene glycol monoethyl ether acrylate)/(undecyl dithiolethanol) (PAAc-g-TEG/SSUD) graft copolymer demonstrated GSH-dependent intracellular release of DOX as well as GSH-dependent cytotoxicity in MCF-7 cells [60]. PAAc-g-mPEG/SS-PTX conjugates with PTX linking to PAAc backbone via a disulfide bond self-assembled into about 60 nm micelles, which exhibited obvious cytotoxicity to OS-RC-2 kidney tumor cells while low cytotoxicity to normal macrophage cells [61]. This was explained by possibly higher GSH concentration in OS-RC-2 tumor cells than normal macrophage cells. Zhang *et al.* reported that reduction-sensitive biodegradable micelles based on poly(aspartic acid)-g-SS-mPEG/6-mercaptopurine (PAsp-g-SS-mPEG/6-MP) while stable in PBS, were prone to aggregation in response to DTT [62]. 6-MP was released in a sustained manner over 85 h in the presence of 40 mM DTT. Moyuan *et al.* reported that apparent diffusion coefficient of DOX from reduction-sensitive chitosan-g-SS-PCL micelles was improved from 1.132×10^{17} cm^2/s to 1.542×10^{17} cm^2/s on addition of DTT [63]. pH and reduction dual-sensitive micellar nanoparticles based on poly(2-(pyridin-2-yldisulfanyl)ethyl acrylate)-g-PEG/cRGD (PPDSEA-g-PEG/cRGD) were stable under physiological condition, while rapidly released DOX in response to 10 mM GSH and/or acidic pH [64]. DOX-loaded PPDSEA-g-PEG/cRGD nanoparticles exhibited enhanced

cellular uptake and nuclear localization in HCT-116 colon cancer cells than PDS-g-PEG controls. The IC_{50} of DOX-loaded PPDSEA-g-PEG/cRGD nanoparticles was comparable with that of free DOX (0.3 vs 0.27 μM). Very recently, Chen *et al.* reported that PCL-g-SS-PEG graft copolymers self-assembled into robust reduction-sensitive micellar nanoparticles with a low CMC in water [65]. DOX-loaded nanoparticles induced pronounced antitumor activity to HeLa cells with an IC_{50} close to that for free DOX.

3. Reduction-sensitive disulfide-crosslinked micellar nanoparticles

In addition to slow intracellular drug release, low *in vivo* stability that leads to premature drug release and diminishing drug accumulation in the tumor sites is another critical issue for current micellar drug formulations. In the past several years, reversible disulfide-crosslinking has emerged as an attractive strategy to elegantly resolve the extracellular stability and intracellular drug release dilemma of micellar drugs [66]. Depending on the location of crosslinking, disulfide-crosslinked micelles could be classified into shell and core-crosslinking (**Table 2**).

3.1 Reduction-sensitive core-crosslinked micellar nanoparticles

Li *et al.* reported that disulfide core-crosslinked (CCL) micellar nanoparticles based on dextran-g-lipoic acid conjugates exhibited high stability and minimal DOX release (ca. 10% in 11 h) under extensive dilution [67]. However, under a reducing environment containing 10 mM DTT, over 90% of DOX was released in 11 h. Confocal microscopy observed rapid and efficient release of DOX into cell nuclei from CCL nanoparticles. More recently, reduction-sensitive CCL micelles were developed from PEG-b-poly(*N*-(2-hydroxypropyl) methacrylamide)-lipoic acid (PEG-b-PHPMA-lipoic acid) conjugates [68]. MTT assays revealed that DOX-loaded CCL micelles retained high antitumor activity to HeLa and HepG2 cells with low IC_{50} of 6.7 and 12.8 μg DOX/ml, respectively, following 48 h incubation. Zhang *et al.* prepared thermo and reduction dual-sensitive CCL micelles from PEO-b-poly(NIPAM-co-*N*-acryloxysuccinimide) (PEO-b-P (NIPAM-co-NAS) copolymer by increasing its aqueous solution temperature to 40°C (above its LCST) followed by crosslinking with cystamine [69]. These dual-sensitive CCL micelles displayed tunable swelling/deswelling behavior with temperature. In a following study, disulfide-crosslinked thermo-responsive CCL micelles were prepared in a one-pot manner via reversible addition-fragmentation chain transfer (RAFT) polymerization of NIPAM and *bis*(2-methacryloyloxyethyl) disulfide (DSDMA) using poly(2-aminoethylmethacrylamide) (PAEMA) as a macro-RAFT agent [70]. These CCL micelles dissociated into unimers on addition of DTT at room temperature. Zhang *et al.* obtained reduction-sensitive CCL micelles by self-assembling of poly(PEG methyl ether methacrylate)-block-poly(5′-*O*-methacryloyluridine) (PPEG-MEMA-b-PMAU) in water followed by crosslinking with DSDMA by RAFT polymerization [71]. It was found that the lower the crosslinking degree and the higher the DTT concentration, the faster transformation of CCL micelles into free block copolymers. The *in vitro* release studies showed that about 60 – 70% of riboflavin was released in 7 h under a reductive condition containing 0.65 mM DTT, whereas only about 30% drug was released in the absence of DTT under otherwise the same conditions. DOX-conjugated CCL micelles were prepared from PHPMA-b-poly(2-(2-pyridyldisulfide)ethylmethacrylate) (PHPMA-b-PPDSEMA) block copolymers by simultaneous DOX conjugation to the micellar core via acid cleavable hydrazone bonds and core-crosslinking via disulfide bonds under catalysis of tri(2-carboxyethyl)phosphine (TCEP) [72]. These CCL micelles disintegrated into unimers in methanol following incubation with excess TCEP; 72% of DOX was released from CCL PHPMA-b-PPDSEMA micelles at pH 5.0 after 23.5 h. By contrast, only 22% of DOX was released at pH 7.4 even after 48 h. pH and reduction dual-sensitive DOX-conjugated CCL micelles were also developed from PEG-b-poly(methacrylic acid-g-hydrazone-DOX) PEG-b-P(MA-g-Hyd-DOX) copolymer using dithiodiethanoic acid as a crosslinker [73]. The results showed that the fastest DOX release was achieved in the presence of both stimuli (pH 4.0 and 15 mM DTT). Kim *et al.* developed disulfide-crosslinked CCL ionic micelles from PEO-b-PMA block copolymers using divalent metal cations (Ca^{2+}) as templates followed by crosslinking with cystamine [74]. These CCL micelles exhibited a high level of DOX loading (50% w/w) due to the ionic interactions between DOX and micellar core. DOX-loaded disulfide-crosslinked PEO-b-PMA micelles demonstrated much higher cytotoxicity with IC_{50} at least six times lower than irreversibly crosslinked counterparts in human A2780 ovarian cancer cells. Heffernan and Murthy designed disulfide-crosslinked polyion micelles by electrostatic self-assembly of 2-pyridyldisulfide (PDS)-functionalized negatively charged proteins with PEG-b-poly(L-lysine-PDS) (PEG-b-PLys-PDS) block copolymer followed by crosslinking using 3,6-dioxa-1,8-octanedithiol (DODT) via disulfide exchange reaction [75]. These crosslinked micelles demonstrated high stability in serum and were explored for controlled delivery of vaccines including ovalbumin and immunostimulatory CpG-DNA.

Li *et al.* reported that disulfide-crosslinked micelles based on thiolated telodendrimers comprised a linear PEG and a cysteine-containing dendritic cluster of cholic acids (CA), PEG-b-Cys_4-Lys_8-CA_8, had superior PTX-loading capacity, enhanced micellar stability, prolonged *in vivo* circulation time and preferential accumulation at the tumor site in nude mice bearing SKOV-3 ovarian cancer xenograft [76]. The release of PTX from micelles while inhibited by crosslinking could be gradually facilitated under a reductive environment. This disulfide-crosslinked micellar PTX exhibited more effective tumor growth inhibition and longer

survival time at a dose of 10 mg PTX/kg than the non-crosslinked (NCL) counterparts and taxol. Yan *et al.* prepared thiol-functionalized biodegradable copolymer, PEG-b-(LA-co-MTC_{SH}), from ring-opening copolymerization of L-lactide and 2-(2,4-dinitrophenylthio)ethyl-5-methyl-2-oxo-1,3-dioxane-5-carboxylate (MTC) using mPEG as a macroinitiator followed by reacting with 2-mercaptoethanol [77]. CCL micelles were readily obtained by self-assembling of PEG-b-(LA-co-MTC_{SH}) in aqueous solution and oxidation of thiols. DOX-loaded CCL micelles exhibited GSH-dependent drug release and cell proliferation inhibition. Abdullah Al *et al.* developed CCL micelles based on thiolated Pluronic F127 bearing thiol groups in the poly(propylene oxide) (PPO) block [78]. The fluorescence intensity of quantum dot (QD)-loaded micelles while maintained in the presence of 10 μM DTT even after 96 h decreased significantly after treatment with 30 and 70 mM DTT. PTX-loaded CCL micelles exhibited a cell viability of 39% in A549 cells at a PTX dosage of 1.5 μg/ml after 24 h incubation, which was comparable with that of free PTX. In a following study, pH and reduction dual-sensitive CCL micelles containing a pH-responsive benzoic-imine bond and disulfide crosslinker were prepared based on Pluronic F127 for taxol delivery [79]. These dual-sensitive CCL micelles showed markedly enhanced QD and taxol release at higher DTT concentration or lower pH. Taxol-loaded CCL micelles induced about 78% cell death to A549 cells after 24 h incubation at a dosage of 1 μg/ml. PEG-b-poly(Tyr(alkynyl)-OCA) micelles containing alkynyl groups in the core (Tyr(alkynyl)-OCA: 5-(4-(prop-2-yn-1-yloxy)benzyl)-1,3-dioxolane-2,4-dione) were facilely crosslinked via click reaction with *bis*-(azidoethyl) disulfide [80]. The release of Nile red could be controlled by ratios of disulfide crosslinker to irreversible crosslinker. Wang *et al.* reported that partially azidated PEG-b-poly(CL-co-(5,5-dibromomethyl trimethylene carbonate)) (PEG-b-PDBTCL-N_3) formed star-shaped CCL micellar nanoparticles (27.3 nm in water and 54.3 nm in DMF) via click reaction with propargyl 3,3′-dithiopropionate [81]. These CCL nanoparticles could undergo dissociation either by reductive cleavage of disulfide bond or by hydrolysis of poly (ester carbonate) core. Cajot *et al.* synthesized three types of amphiphilic copolymers, PEO-b-P(CL-co-(α-N_3CL)), PEO-b-PCL-b-P(α-N_3CL) as well as PEO-b-P(α-N_3CL)-b-PCL by ring-opening polymerization of ε-CL and azide-functionalized CL (α-N_3CL) using PEO as a macroinitiator [82]. These three copolymers formed reduction-sensitive loosely core-crosslinked, tightly core-crosslinked and shell-crosslinked (SCL) micelles, respectively, using *bis*(ethyl-4-pentynoate) disulfide (BEPDS) as a crosslinker.

3.2 Reduction-sensitive shell-crosslinked micellar nanoparticles

Koo *et al.* reported reduction-sensitive SCL polypeptide micelles via self-assembly of PEG-b-PLys-b-poly(L-phenylalanine) (PEG-b-PLys-b-PPhe) triblock copolymer in water followed by crosslinking with 3,3′-dithiobis(sulfosuccinimidylpropionate) (DTSSP) [83]. The *in vitro* release studies revealed that shell-crosslinking greatly inhibited methotrexate (MTX) release. The release of MTX increased, however, with increasing GSH concentration in the media. The cytotoxicity of MTX-loaded SCL micelles exhibited a clear correlation with the intracellular GSH levels in A549 cells. The *in vivo* studies in MDA-MB-231 tumor bearing mice demonstrated that docetaxel (DTX)-loaded SCL PEG-b-PLys-b-PPhe micelles more effectively inhibited tumor growth than NCL controls (**Figure 2A**) [84]. The biodistribution studies showed that fluorescence was detected following 2 days injection of Cy5.5-labeled SCL micelles while rapid decrease of fluorescence was observed for Cy5.5-labeled NCL micelles (**Figure 2B**). Jiang *et al.* prepared indomethacin (IND)-loaded SCL nanoparticles by one-pot RAFT polymerization of styrene (St) and *bis*(acryloyloxyethyl) disulfide (BAEDS) using PDEAEMA-$C_{12}H_{25}$ as a macro-RAFT agent [85]. The release of IND was shown to be dependent on GSH and pH. Yue *et al.* developed SCL micelles from Y-shaped PEG-b-PLG-b-$(PLA)_2$ block copolymers using cystamine as a crosslinker [86]. These SCL micelles exhibited enhanced DOX loading efficiency and better *in vitro* stability than NCL counterparts. Moreover, DOX-loaded SCL micelles showed similar cytotoxicity in HeLa cells as well as longer blood circulation *in vivo* as compared with free DOX and NCL micelles. Tao *et al.* prepared SCL Pluronic micelles based on thiolated Pluronic F127 and P123 using gold nanoparticles as a crosslinker (Au-PF-PTX) for PTX delivery [87]. Au-PF-PTX SCL micelles exhibited higher antitumor activity against GSH-OEt pretreated U87 cells than non-treated cells. *In vivo* studies revealed that Au-PF-PTX SCL micelles were more stable than NCL PF-PTX micelles, and were primarily accumulated in spleen and liver after 24 h i.v. injection.

Zhang and Zhao prepared SCL micelles by crosslinking alkynylated surfactant with disulfide-containing diazide [88]. The incorporated pyrene was completely released in < 1 min from disulfide-crosslinked micelles on addition of 1 equiv. or 20 μM DTT, which was much faster than acetal-crosslinked micelles at low pH. Xu *et al.* found that interfacially crosslinked micelles based on PEG-PCL diblock copolymer with two lipoyl groups at its junction (PEG-L_2-PCL) showed markedly enhanced stability against dilution, while released DOX rapidly in response to 10 mM DTT with about 75% release in 9 h [89]. Kim *et al.* prepared reduction-sensitive SCL micelles based on PEG-PCL diblock copolymer with three cysteine residues at its junction (PEG-Cys_3-PCL) [90]. These SCL micelles effectively prevented disassociation on dilution. The introduction of 1 mM DTT, however, resulted in burst release of DOX. Lee *et al.* reported that SCL biodegradable micelles based on PEG-Cys_4-PDLLA copolymer stably retained DOX during circulation and delivered seven fold higher drug to the tumor while 1.9-fold lower in the heart as compared with NCL PEG-b-PDLLA micelles [91]. DOX-loaded crosslinked

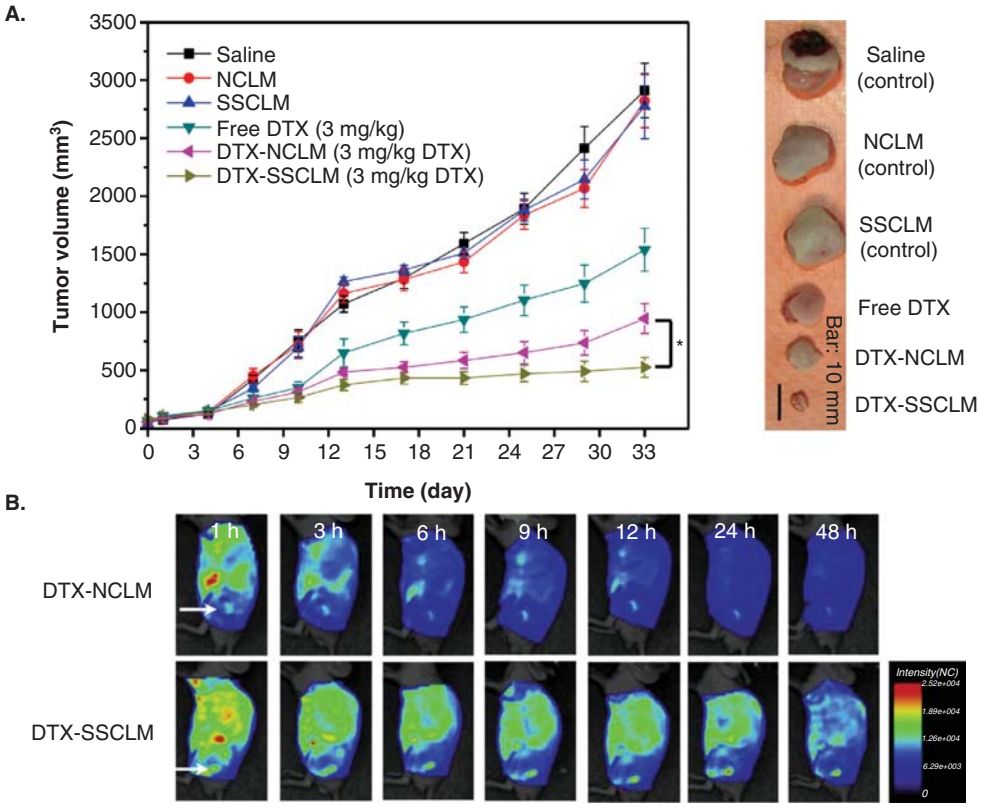

Figure 2. Disulfide-crosslinked micelles based on PEG-b-PLys-b-PPhe for *in vitro* and *in vivo* DTX delivery. (**A**) Changes in tumor volumes after injection of saline, NCLM, SSCLM, free DTX, DTX-NCLM and DTX-SSCLM, respectively. The results represent the means – SD (n = 6). *p < 0.05. (**B**) *In vivo* non-invasive NIRF images of time-dependent whole body imaging of MDA-MB-231 tumor-bearing mice after i.v. injection of Cy5.5-DTX-NCLM and Cy5.5-DTX-SSCLM. Solid arrows indicate the tumors.

Reproduced with permission from Elsevier [84].

PEG-Cys_4-PDLLA micelles almost completely inhibited M109 tumor growth in mice within 14 days after initial treatment with 2 mg DOX/kg at day 0 and 4. DOX-loaded SCL PEG-b-PCys-b-PPhe micelles were successfully internalized into HeLa cells after 4 h incubation and induced higher cytotoxicity to 20 mM GSH-OEt pretreated HeLa cells as compared with non-treated cells [92]. In a similar way, reduction-sensitive SCL micelles demonstrating enhanced stability during circulation and accelerated intracellular drug release were also obtained from PEG-b-PPE_{SH}-b-PCL (PPE_{SH}: polyphosphoester with side thiol groups) triblock copolymer [93].

Dai *et al.* reported pH and reduction dual-sensitive SCL micelles based on PEG-b-poly(Asp-g-2-mercaptoethylamine)-b-poly[Asp-g-2-(diisopropylamino)ethylamine] (PEG-b-PAsp(MEA)-b-PAsp(DIP)) triblock copolymer [94]. These crosslinked micelles were stable with low drug leakage during storage and blood circulation while gave a burst drug release under an acidic and reductive condition (about 95% release in 5 h). Furthermore, *in vivo* studies via measuring tumor size, body weight and survival rate revealed that DOX-loaded dual-sensitive SCL micelles had better therapeutic effects than free DOX and DOX-loaded PEG-PCL micelles. Reduction and pH dual-sensitive SCL micelles were also constructed from PEO-b-poly(*N*-(3-aminopropyl) methacrylamide)-b-poly(2-(diisopropylamino)ethyl methacrylate) (mPEO-b-PAPMA-b-PDPAEMA) triblock copolymer in water by adjusting pH to above 6.0 and subsequent crosslinking with dimethyl 3,3′-dithiobispropionimidate (DTBP) [95]. These SCL micelles were efficiently de-crosslinked in the presence of 9.4 mM DTT after 1 h.

4. Conclusion

The past several years has witnessed an explosive development of reduction-sensitive micellar nanoparticles from different types of amphiphilic copolymers for triggered intracellular release of potent anticancer drugs. These 'active' drug delivery systems have demonstrated clearly improved *in vitro* antitumor efficacy as compared with reduction-insensitive controls. In particular, disulfide-crosslinked micellar nanoparticles have appeared to simultaneously meet the conflicting requirements of high stability and fast intracellular drug release for cancer

therapy. The several *in vivo* studies confirm that disulfide-crosslinked micellar anticancer drugs have accomplished prolonged circulation time, improved accumulation at the tumor tissue and better tumor inhibition. These reduction-sensitive degradable micellar nanoparticles have been established as an advanced and yet practical platform for targeted cancer chemotherapy.

5. Expert opinion

Reduction-sensitive degradable micellar nanoparticles though experience so far only a few years of research and development have demonstrated a tremendous potential in targeted and active intracellular delivery of poorly soluble anticancer drugs including PTX, DOX and MTX. As compared with pH-sensitive nanoparticles which are the most studied stimuli-sensitive systems for triggered drug release, reduction-sensitive micellar formulations have unique advantages of high stability against hydrolytic degradation, fast response to intracellular reducing environment and triggering drug release right in the cytosol and cell nucleus where many anticancer drugs take effects. The *in vitro* studies in various tumor cells have clearly pointed out that reduction-responsive drug release significantly boosts antitumor efficacy, which is approaching and in several cases surpassing that of free drugs. The crosslinking of micellar nanoparticles via reversible disulfide bonds has on one hand resulted in enhanced stability, prolonged drug circulation time and inhibited premature drug release following i.v. injection and on the other hand enabled fast de-crosslinking and/or dissociation of micelles inside cancer cells, leading to efficient tumor-targeting delivery and release of anticancer drugs. This reduction-sensitive reversible crosslinking approach has provided an elegant and yet straightforward solution to the long-standing stability and drug release dilemma of nanoparticulate drug formulations. It should be noted that reduction-sensitive degradable polyplexes [96] and more recently polymersomes [97,98] have successfully been developed for enhanced intracellular delivery of DNA and protein drugs, respectively.

The exceptional attributes of reduction-sensitive degradable micellar nanoparticles warrant further research and development. For example, it remains unclear where exactly in cancer cells and to which extent degradation of disulfide bonds takes place. While most results show that reductive degradation occurs in the cytosol, several studies indicate that disulfide is degraded in the lysosomes. Moreover, vastly different drug release rates, in which drug is released in a time scale varying from minutes, hours to days, have been reported for different systems. It is evident that the disulfide microenvironment in particular hydrophilicity and thereby accessibility of glutathione tripeptides plays a critical role. The exact factors governing degradation of reduction-sensitive micellar nanoparticles have, nevertheless, not been systematically investigated. The insight into reductive degradation behavior would facilitate rationale design of advanced drug nanocarriers. In terms of disulfide-crosslinked micellar nanoparticles, influences of extent and position (core, shell or interface) of crosslinking on *in vivo* antitumor efficacy should be studied.

In order to advance to the clinical applications, multifunctional reduction-sensitive degradable micellar nanoparticles should be developed. First of all, all constituent materials should be biocompatible and degradable into non-toxic products that can further be excreted or absorbed by human body. As brand-new materials are difficult to obtain Food and Drug Administration (FDA) approval, reduction-sensitive micellar nanoparticles are best made of traditional degradable materials with proven safety. Second, reduction-sensitive degradable micellar nanoparticles should possess high drug loading capacity, which on one hand significantly reduces use of carrier materials and on the other hand may maximize drug efficacy. It is found that introduction of ionic interactions between drug and carrier can largely improve drug loading levels [99,100]. Finally, reduction-sensitive degradable micellar nanoparticles should be decorated with a targeting ligand that facilitates specific and efficient tumor cell uptake. It should be noted that disulfide chemistry is particularly robust and versatile, which enables facile design and development of functional nanocarriers to ideally suit targeted cancer chemotherapy. These reduction-sensitive degradable micellar anticancer drug formulations with fast and efficient drug release in the target cancer cells act as novel 'drug bomb' that may effectively treat various tumors including MDR tumors.

Declaration of interest

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