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ARTICLE

Noncovalent interaction-assisted polymeric micelles for controlled drug delivery

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Polymeric micelles are one type of the most promising nanovehicles for drug delivery. In addition to amphiphilicity, various individual or synergistic noncovalent interplays including strong hydrophobic, electrostatic, host-guest, hydrogen bonding, stereocomplex and coordination interactions are recently employed to improve the physical stability of micelles, and even provide them with certain intelligences or bioactivities. Through the ingenious designs and precise preparations, plenty of noncovalent-mediated micelles display great prospects in the realm of controlled drug delivery, and certain of species have been promoted to clinical trials. The current review presents the diverse noncovalent interactions that are applied to update the polymeric micelles as drug nanocarriers, and preliminarily discuss the future directions and perspectives of this field.

1. Introduction

Polymeric micelles are one kind of the submicroscopic colloids, which originate from the spontaneous self-assembly of amphiphilic copolymers in aqueous environment.^{1–3} The micelles typically exhibit the core-shell architectures, and the inner cores and outer shells are respectively composed of the hydrophobic blocks and hydrophilic segments of amphiphiles.^{1,2,4} The micellization of copolymers is a process of entropy-driven microphase separation, and forms the aggregations with an average diameter range of 5 – 100 nm in most instances.^{5–8}

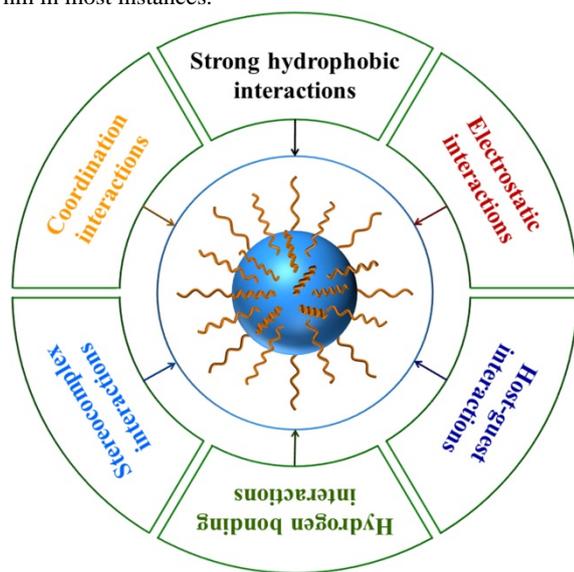


Fig. 1 Noncovalent interactions for updating polymeric micelles.

Since 1984, polymeric micelles have been an emerging platform for the smart delivery of poorly water-soluble or amphiphilic

drugs.^{9–11} In this basic and common application, the hydrophobic cores serve as the reservoirs of bioactive agents, whereas the hydrophilic shells provide the necessary hydrophilicity, stabilize the cores and maintain the dispersion of micelles. Moreover, polymeric micelles possess a series of remarkable merits as drug nanocarriers: 1) great diversity of matrix copolymers, 2) various surface functional groups and facile modification, 3) sufficient drug loading content and efficiency, 4) long circulation time and half-life in the circulatory system, 5) high accumulation in the lesion sites, 6) tunable degradation time for controlled drug delivery, 7) remittent severe side-effects, and 8) desirable bioavailability and therapeutic effect, *et al.*^{12–14} The above fascinating characteristics endow micelles with great potential for *i.v.* drug delivery, and several micellar formulations are under clinical trials (*e.g.*, BIND-014,¹⁵ NC-4016,¹⁶ NC-6004,^{17,18} NK105¹⁹ and SP1049C²⁰) or even already on the market (*e.g.*, Genexol[®]-PM).²¹

Although the micelle-based drug delivery systems have made great progress in the past few decades, the stability of polymeric micelles has been a principal challenge for further in-depth application as nanovehicles because the polymeric chains are in a dynamic equilibrium shuttling between micelle and the bulk phase.^{22–24} Inspired by the living organisms in nature (*e.g.*, viruses, bacteria and cells), the noncovalent interactions, such as strong hydrophobic,²⁵ electrostatic,^{26,27} host-guest,²⁸ hydrogen bonding²⁹, stereocomplex³⁰ and coordination interactions³¹ or their combinations,³² have been introduced into polymeric micelles to endow them with enhanced stability, and certain accessional intelligences and bioactivities (Fig. 1). In this review, the advances of noncovalent interaction-stabilized micellar nanocarriers were systematically presented, and the probable challenges and development prospects were briefly forecasted.

2. Noncovalent interactions employed in smart nanocarriers

Amphiphilicity is the most primitively and commonly applied driving force for the micellization of copolymers in aqueous solution.^{33,34} Typically, the hydrophobic segments incline to hide from the aqueous phase becoming the micellar core, while the hydrophilic segments in the amphiphilic copolymers tend to combine with water molecules forming the micellar shell.²⁶ However, the amphiphilicity is weak and restricted to prepare the stable

micelles, which exhibit a more broad application in the field of drug delivery.³ As above emphasized, the noncovalent interactions play an important role in the improvement of micellar platforms for smart drug delivery, and the properties were summarized and listed in Table 1.^{35,36} In the main text, the noncovalent interaction-mediated micellar nanocarriers were classified and reviewed.

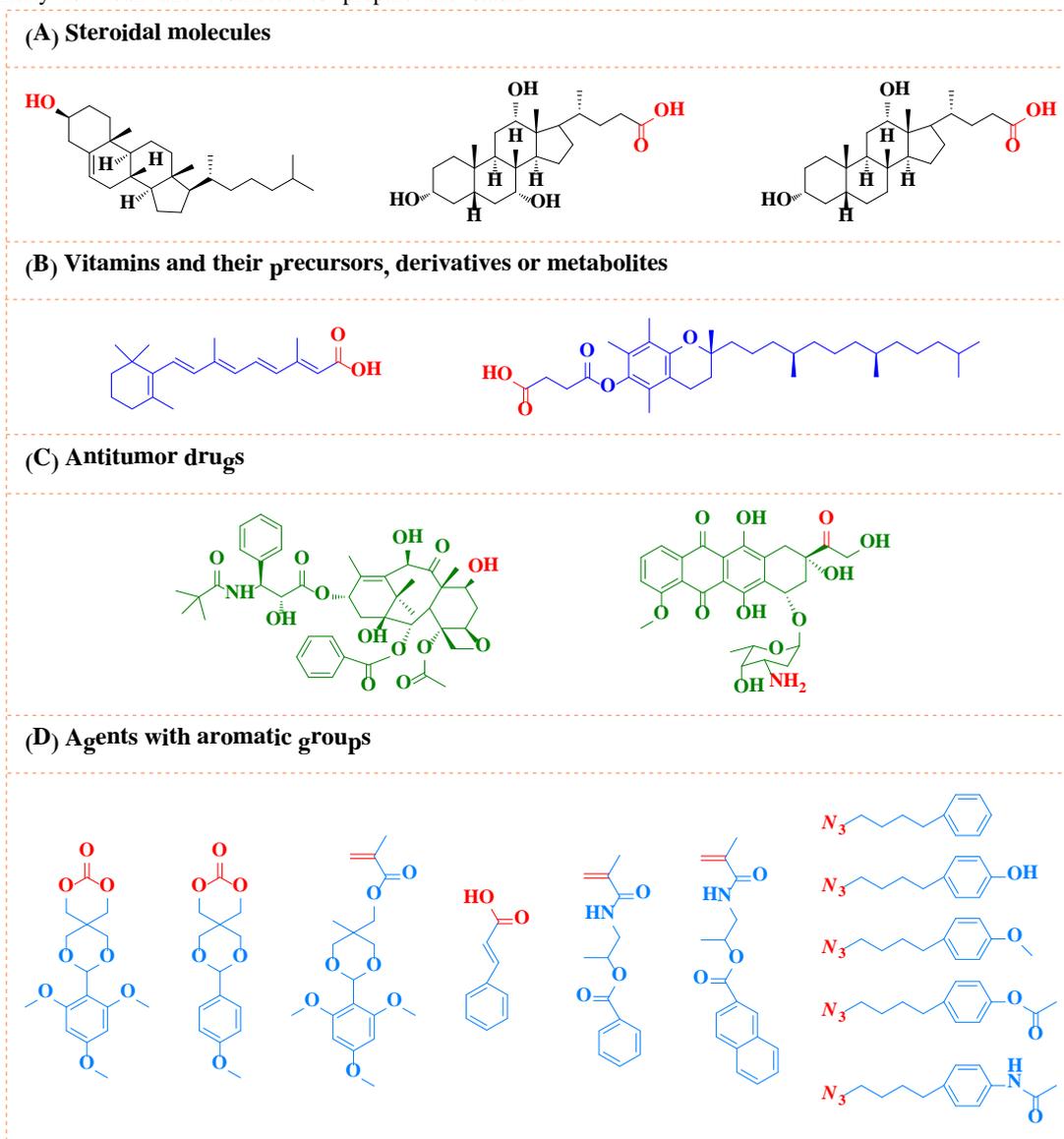


Fig. 2 Chemical structures of typical large hydrophobic agents serving in strong hydrophobic interactions. The red parts were reactive groups.

Table 1 Properties of noncovalent interactions^{35,36}

Species	Strength (kJ mol ⁻¹) ^a	Characters	
Amphiphilicity	< 50	Nonselective and nondirectional	and
Strong hydrophobic interactions	5 – 50	Nonselective and nondirectional	and
Electrostatic interactions	5 – 100	Nonselective	
Host-guest interactions	10 – 100	Extremely selective	
Hydrogen bonding interactions	5 – 150	Selective and directional	
Stereocomplex interactions	~ 5	Nonselective and nondirectional	and
Coordination interactions	50 – 200	Directional	
Covalent interactions	200 – 1000	Irreversible	

^a The interaction energy in most cases.

2.1. Strong hydrophobic interactions

In this review, strong hydrophobic interaction is defined as one kind of hydrophobic interactions originated from the large hydrophobic or aromatic groups, which is the elongation of typical amphiphilicity.^{37,38} As depicted in Fig. 2, the large hydrophobic agents, such as cholesterol,^{25,39} cholic acid (CA),^{40,41} deoxycholic acid (DCA),^{42,43} all-trans retinoic acid (ATRA),⁴⁴ vitamin E (VE, *i.e.*, α -tocopherol),⁴⁵ paclitaxel (PTX),^{46,47} doxorubicin (DOX)^{48,49} or aromatic groups,^{38,50} were conjugated or introduced to the hydrophilic or amphiphilic copolymers to enhance the stability of micelles or provide certain bioactivities.

2.1.1. Hydrophobic interactions based on steroidal molecules. The hydrophobic steroidal molecules (formula weight (FW) = 300 –

500 g mol⁻¹) including cholesterol, CA, DCA, *etc.* are the most commonly used agents to form or stabilize the micellar cores. Beginning in 1993, Akiyoshi and coworkers have bound cholesterol to pullulan yielding the amphiphilic polysaccharides, which could self-assemble into stable micelles "cross-linked" by the association of hydrophobic groups.⁵¹⁻⁵³ Subsequently, cholesterol was conjugated to the thermo-responsive random poly(*N*-isopropylacrylamide-*co*-*N*-hydroxymethylacrylamide) by He *et al.*⁵⁴ The resultant amphiphilic graft copolymer formed into micelle that could be developed for the controlled delivery of hydrophobic drugs. In Yang's group, the cholesterol-modified cyclic carbonate monomer was synthesized, and the amphiphilic block copolymers composed of methoxy poly(ethylene glycol) (mPEG) and polycarbonate were synthesized by the metal-free organocatalytic ring-opening (co)polymerization of nonfunctionalized or functionalized monomers.²⁵ PTX was loaded into micelles through nanoprecipitation with optimal sub-50 nm scale and high loading capacity (15 wt.%). The preferred PTX-loaded micelles exhibited enhanced antiproliferative efficacies toward HepG2 (a human hepatoma cell line) and 4T1 cells (a mouse breast cancer cell line) compared with free PTX, and effective passive accumulation in tumor tissue. Recently, Chen and colleagues synthesized a series of well-defined amphiphilic linear-dendritic copolymers with 1, 2, 4 or 8 terminal cholesterol.³⁹ The telodendrimers spontaneously formed into micelles, and encapsulated PTX and DOX for synergistic therapeutic. The micelle with 8 terminal cholesterol exhibited the most appropriate drug loading efficiency (DLE) and a controlled release manner for both PTX and DOX. The better antitumor efficacy of codelivery system than the single drug platform against HepG2 and MCF-7 cells (a human breast cancer cell line) was demonstrated.

CA and DCA are the other two universal steroidal matrices for stable micelle fabrication. Kim, Jeong *et al.* synthesized the CA-modified glycol chitosan as the carrier of camptothecin (CPT) with high DLE (> 80 wt.%).⁵⁵ The CPT-loaded micelle presented sustained CPT release for 1 week and significant antitumor efficacy against subcutaneously MDA-MB-231 human metastatic breast cancer xenografted nude mice at doses of 10 and 30 mg kg⁻¹ compared with free CPT at a dose of 30 mg kg⁻¹. Moreover, CA was linked to the end of linear and linear-dendritic copolymers to improve the stability and PTX loading efficacy by in Shuai's, and Luo and Lam's groups, respectively.^{40,56-58} As shown in Fig. 3, the pH-responsive multifunctional micelle based on folic acid-polyethylene glycol-poly(*N*-(*N*',*N*'-diisopropylaminoethyl) aspartamide)-cholic acid (FA-PEG-PAsp(DIP)-CA) copolymer was prepared for the tumor-targeted programmed intracellular drug release and fluorescent imaging.⁵⁶ Both the cell and animal assays against Bel-7402 cells (a human hepatoma cell line) demonstrated that the targeting micelle exhibited enhanced selective accumulation and tumor growth inhibition. Luo, Lam and coworkers synthesized the telodendrimers composed of PEG, CA and lysine for PTX delivery.^{57,58} The PTX-loaded micelle showed similar *in vitro* cytotoxic activity toward SKOV-3 cells (a human ovarian cancer cell line) as Taxol[®] (free PTX) and Abraxane[®] (paclitaxel/human serum albumin nanoaggregate), while exhibited 2.5-fold higher maximum tolerated dose (MTD) than that of Taxol[®]. Benefited from the preferential accumulation and deep penetration in tumor tissue, the PTX-loaded micelle presented the superior antitumor effects in both subcutaneous and orthotopic intraperitoneal SKOV-3 xenografted murine models compared with Taxol[®] and Abraxane[®]. Furthermore, the slightly negatively charged micelle was demonstrated to exhibit enhanced uptake at tumor site but not normal organs.⁴⁰ In addition, DCA were bound to pullulan, glycidol-chitosan and carboxymethylated chitosan for preparing the pH-responsive

micelles as nanocarriers of DOX or PTX in Bae's, and Ma and Zhang's groups, respectively.^{43,59,60} All the drug-loaded DCA-functionalized polysaccharide micelles exhibited the pH-dependent releasing kinetics and the similar inhibition capability of the proliferation of MCF-7 cells as free drugs. More interestingly, the disulfide bond bridged deoxycholic acid-hyaluronic acid (DCA-HA) was synthesized and employed for targeted intracellular PTX delivery by Huo and coworkers.⁴² The reduction-responsive PTX-loaded micelle possessed accelerated PTX release in the presence of 20 mM glutathione (GSH) and improved uptake in MDA-MB-231 cells *via* HA-receptor mediated endocytosis and *in vivo* tumor targeting capability compared with the insensitive control.

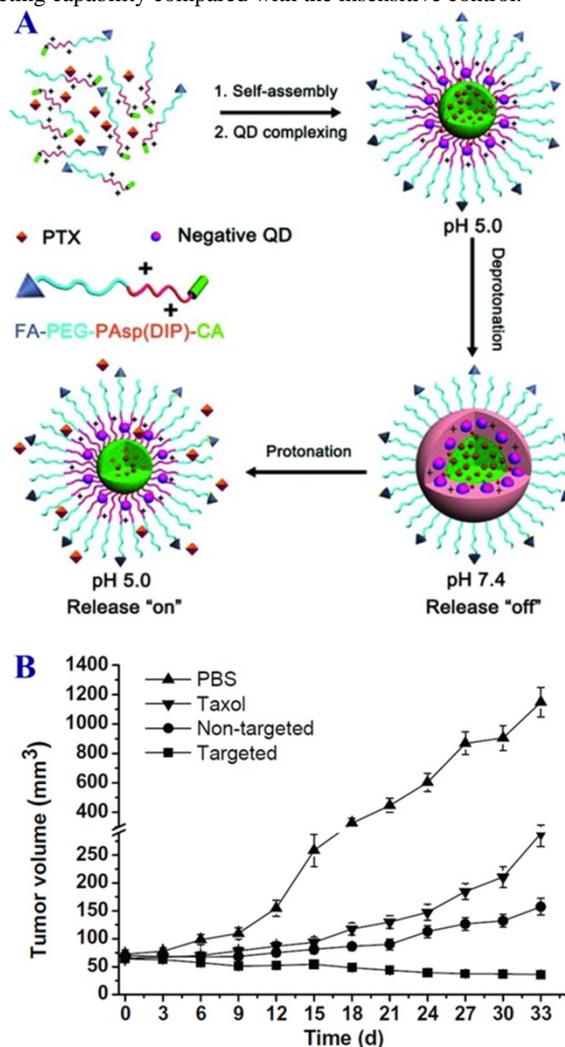


Fig. 3 (A) Schematic illustration of PTX and quantum dot (QD)-loaded micelle preparation and pH-tunable drug release; (B) *in vivo* tumor growth inhibition of Taxol[®], non-targeted and targeted PTX-loaded micelles (dose: 1 mg PTX per kg body weight through tail vein injection for PTX-containing formulations at an interval of 3 days) toward Bel-7402 tumor xenografted nude mice ($n = 20$).⁵⁶

2.1.2. Hydrophobic interactions of vitamins associated molecules. Vitamins and their precursors, derivatives or metabolites are another hydrophobic ligands used for heighten the micellar systems. Of them, ATRA and VE are the commonly used agents.^{44,45} ATRA, a non-toxic physiological metabolite of vitamin A, is reported to redirect the malignant cells into approximate normal blood cells in the process of acute promyelocytic leukaemia treatment. Recently, ATRA was conjugated to the biodegradable methoxy poly(ethylene glycol)-*block*-poly(lactide-*co*-2,2-

dihydroxymethyl propylene carbonate) copolymer as auxiliary matrix of polymer–cisplatin(IV) conjugate micelle for effectively inhibiting the proliferation of SKOV-3 cells *in vitro* and U14 cells (a mouse cervical cancer cell lines) *in vivo*.⁴⁴ Vitamin E succinate (VES), a prototype of VE, was widely developed as antitumor agent against multiple malignancies, including lung, breast and prostate cancers, *et al.*, while almost no toxicities to normal cells.^{61,62} The PEG–VE conjugates with the variations of the number-average molecular weight (M_n) of PEG (2000 or 5000 g mol⁻¹) and the molar ratio of PEG/VE (1:1 or 1:2) were independently synthesized by He, Sun *et al.*, and Li *et al.* for DOX and PTX delivery, respectively.^{63,64} All the PEG–VE conjugates could suppress the P-glycoprotein (P-gp) function effectively. As depicted in Fig. 4, the DOX-loaded micelle with high DLE as 94.5 wt.% was revealed to be effectively internalized into P-gp over-expressed adriamycin-resistant MCF-7 cells (MCF-7/ADR) through macropinocytosis and caveolin-dependent endocytosis, and presented enhanced antitumor efficacy *in vivo* toward 4T1-bearing BALB/C mice (one kind of mouse breast cancer).⁶³ More interestingly, the PTX-loaded PEG5000–VE₂ micelles gave the best tumor growth inhibitory effect compared with PTX-encapsulated PEG2000–VE and PEG2000–VE₂ as well as Taxol[®] in a syngeneic mouse model of breast cancer (4T1.2 cells).⁶⁴

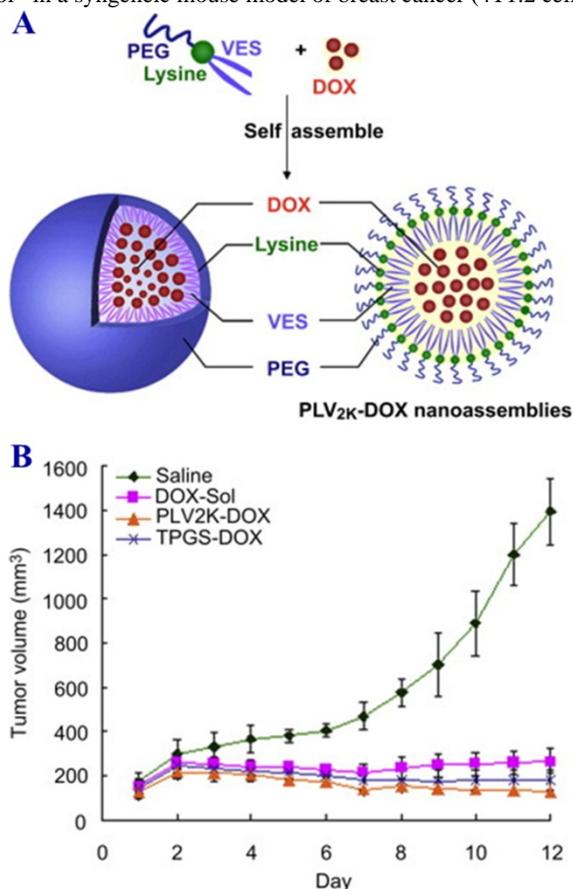


Fig. 4 (A) Schematic preparation of DOX-loaded PEG2000–VE₂ micelle (*i.e.*, PLV2k-DOX nanoassemblies); (B) the antitumor efficacies of DOX-loaded PEG2000–VE₂ micelle against 4T1-bearing BALB/C mice with saline, free DOX (*i.e.*, DOX-Sol) and DOX-loaded PEG1000–VE micelle (*i.e.*, TPGS-DOX) as controls. The *i.v.* administrations were performed on days 1, 4 and 7 at an equivalent dose of 10 mg DOX per kg body weight.⁶³

2.1.3. Hydrophobic interactions between drugs. Furthermore, various hydrophobic antitumor drugs are linked to the hydrophilic or amphiphilic (co)polymers to form or steady the polymeric micelles. The polymer–drug conjugates are also defined as "polymeric prodrugs", which was proposed by Ringsdorf in 1975.⁶⁵ PTX and

DOX are the most commonly applied drugs to fabricate various polymeric prodrugs. Initially, PTX is conjugated to various hydrophilic linear or dendritic polymers (*e.g.*, *N*-(2-hydroxypropyl) methacrylamide (HPMA) copolymers, poly(L-glutamic acid) (PGA), poly(L-γ-glutamylglutamine) (PGG) and hyperbranched poly(ether-ester) (HPEE)) with ester bond to prepare polymer–PTX prodrug micelles.^{66–69} The *in vitro* and *in vivo* experiments are systematically implemented, and several systems, such as HPMA–PTX (PNU 166945)⁶⁶ and PGA–PTX (CT-2103) micelles⁶⁷ are in Phase I (Netherlands, discontinued) and Phase III clinical stages (USA), respectively. Recently, PTX are bound to biodegradable amphiphilic copolymers through ester bond,^{46,70} or pH-responsive ester⁴⁷ or acetal linkage.⁷¹ Jing and coworker bound PTX to biodegradable poly(lactide-*co*-(glycolic acid)-*alt*-(L-glutamic acid))-*block*-poly(ethylene glycol)-*block*-poly(lactide-*co*-(glycolic acid)-*alt*-(L-glutamic acid))₂, and the obtained polymer–PTX micelle maintained a certain ability for inhibiting the proliferation of C6 cells (a rat brain glioma cell line). In Wooley's group, the unresponsive or acid-labile poly(ethylene glycol)-*block*-(polyphosphoester-*co*-(polyphosphoester-*graft*-paclitaxel) (PEG-*b*-(PEEP-*co*-(PEEP-*g*-PTX))) conjugates with high PTX loading capabilities (> 50 wt.%) were synthesized through the combination of ROP and click reaction.^{46,47} The copolymer–PTX prodrugs, especially the pH-responsive one, exhibited effective antiproliferative efficacies toward several test cells, such as, OVCAR-3 (a human ovarian cancer cell line) and RAW 264.7 cells (a mouse monocyte cell line). In addition, Zhong *et al.* prepared the endosomal pH-activatable poly(ethylene glycol)-*block*-poly(acrylic acid)-paclitaxel (PEG-*b*-PAA–PTX) prodrugs with up to 42.8 wt.% PTX adopting the acid-labile acetal linkage.⁷¹ The PTX release from prodrug micelles was pH-dependent, in which *ca.* 86.9, 66.4 and 29.0 wt.% of conjugated PTX was released at pH 5.0, 6.0 and 7.4 in 48 h, respectively. Moreover, the prepared prodrug micelles, especially which with FA, showed some tumor inhibitory activity, and could be potentially used to reverse the multi-drug resistance or as a pH-responsive nanovehicle for controlled delivery of another antitumor drugs.

Similarly, DOX is conjugated to different hydrophilic or hydrophobic polymers, including HPMA copolymers (FCE 28068⁷² and FCE 28069),⁷³ dextran (Dex, AD-70),⁷⁴ polylactide (PLA),⁷⁵ PEG⁷⁶ *et al.*, with amide, Schiff's base or hydrazone bonds. The obtained polymer–DOX prodrugs (*i.e.*, FCE 28068 and AD-70) are in Phase II (UK) and I clinical stages (Germany), respectively.^{72,74} In recent years, DOX is conjugated to the different amphiphilic copolymers that constructed a series of pH-responsive copolymer–DOX conjugates with acid-labile hydrazone or amide bones for potential malignancy therapy.^{49,77–85} For example, Kataoka and coworkers synthesized the poly(ethylene glycol)–poly(aspartate-hydrazone–adriamycin) (PEG–P(Asp–Hyd–ADR)) prodrug with acid-sensitive hydrazone bond as linkage.^{77,78} The intracellular pH-responsive prodrug micelles displayed an acidity-accelerated DOX release profile, presented a higher bioavailability than free DOX and exhibited enhanced therapeutic efficacy toward SBC-3 (a human small cell lung cancer cell line) and C26 cells (a mouse colon cancer cell line) with reduced toxicity. Chen and coworker linked DOX to the terminals of Y- or dumbbell-shaped poly(ethylene glycol)–poly(lactide-*co*-glycolide) (PEG–PLGA) copolymers with pH-responsive amide bone. As show in Fig. 5, the prodrugs formed into micelles in phosphate-buffered saline (PBS) at pH 7.4, and exhibited efficient intracellular DOX release and long-term cellular proliferation inhibition against HepG2 and HeLa cells (a human cervical cancer cell line).

2.1.4. Hydrophobic interactions from aromatic π–π stacking. The π–π stacking between aromatic groups is another kind of strong hydrophobic interactions used for enhancing the stability of micelles.

Zhong and coworkers synthesized the pH-responsive poly(ethylene glycol)–aromatic groups–modified polycarbonates as micellar matrices for the intracellular targeted delivery of PTX or DOX.^{86,87} All the drug-loaded stable micelles exhibited acid-accelerated drug release for both PTX and DOX. In Hammond's group, the poly(ethylene glycol)–poly(γ -propargyl-L-glutamate) copolymers with different hydrophobic side groups were prepared for PTX encapsulation.⁸⁸ The stabilized micelles exhibited tunable physicochemical properties, and the PTX-loaded micelles possessed adjustable PTX release behaviors and antiproliferative capabilities toward HeLa cells. Hennink *et al.* synthesized the aromatic-modified poly(ethylene glycol)–polymethacrylamide copolymers through the free radical copolymerization of *N*-(2-benzoyloxypropyl)

methacrylamide or the corresponding naphthoyl analogue, and *N*-(2-hydroxypropyl) methacrylamide monoactate.³⁸ The supplemented π - π stacking effect resulted from the aromatic groups improved the stability and loading capacity of polymeric micelles. The PTX-loaded micelles exhibited high cytotoxicity against B16F10 cells (a mouse melanoma cell line). Recently, Gu and colleagues prepared the DOX-loaded micelles from the conjugates between DOX and methoxy poly(ethylene glycol)–cinnamic acid (mPEG–CIN) or mPEG–Lys–DCIN *via* π - π stacking interaction.⁵⁰ The DOX-loaded mPEG–Lys–DCIN micelle displayed better stability, higher DLE and slower release rate. In addition, the *in vivo* antitumor activity of DOX-loaded mPEG–Lys–DCIN micelle was comparable to that of free DOX with reduced side effects.

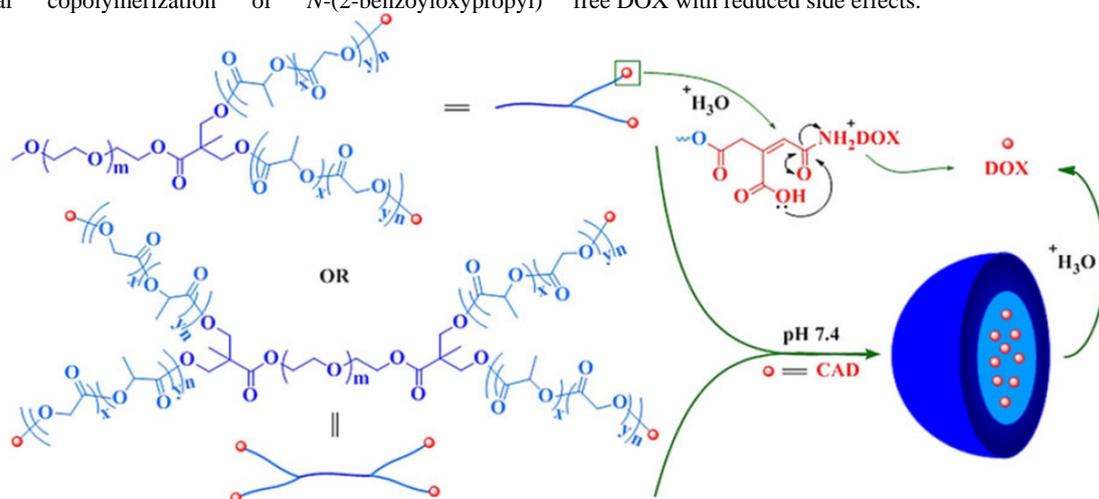


Fig. 5 Chemical structures of Y- or dumbbell-shaped PEG–PLGA–DOX prodrugs and schematic illustration of self-assembly and acidity-triggered DOX release.⁸⁵

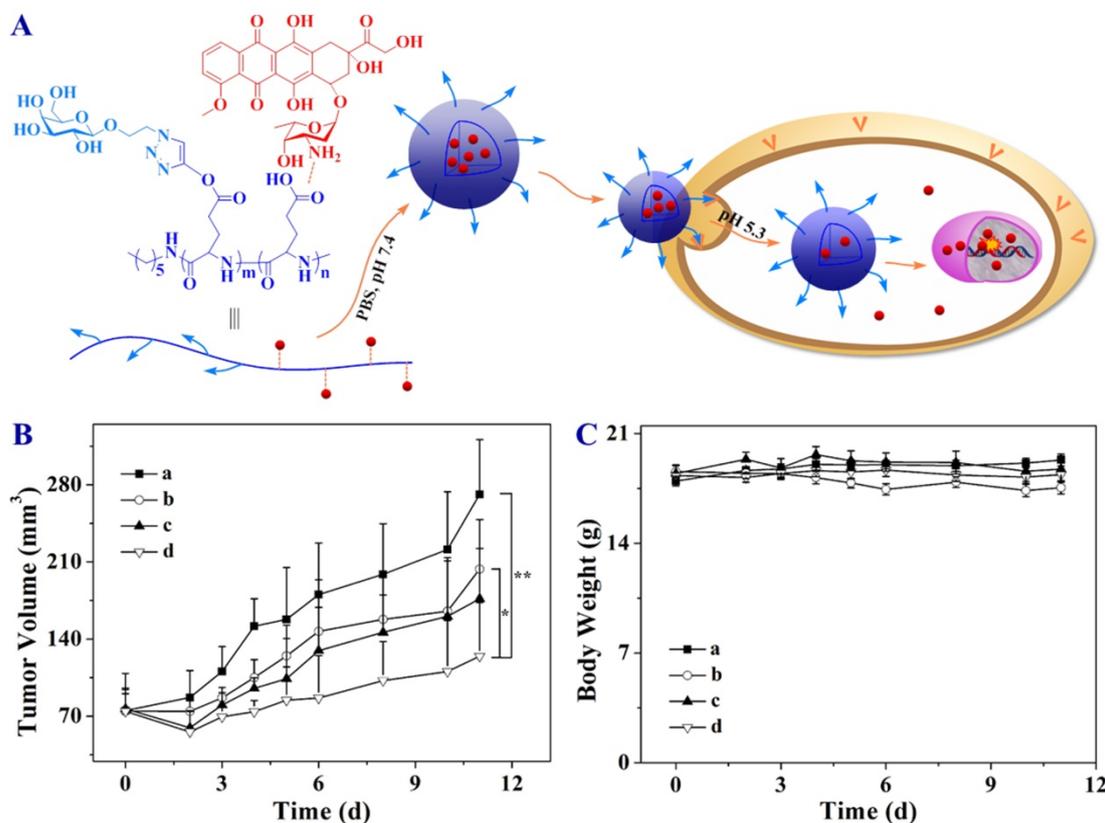


Fig. 6 (A) Schematic illustration of DOX-loaded hepatoma-targeted micelle preparation and intracellular DOX delivery; (B) antitumor efficacy *in vivo* and (C) body weight change of HepG2 human hepatoma xenografted female BALB/c nude mice treated with (a) PBS, (b) free DOX, and (c) DOX-loaded micelles

from poly(OEGylated L-glutamate)₇-*block*-poly(L-glutamic acid)₂₂ and (d) poly(galactosylated L-glutamate)₇-*block*-poly(L-glutamic acid)₂₂. Each formulation was administered on days 0, 3, 6 and 9 by tail-vein injection with a dosage of 2.0 mg DOX per kg body weight for injection of free DOX and DOX-loaded micelles. Data were presented as mean \pm standard deviation ($n = 6$) (* $p < 0.05$, ** $p < 0.001$).^{91,92}

2.2. Electrostatic interactions

The cooperative formation of ionic bond through electrostatic attraction between a pair of oppositely charged matrices is a versatile tractive force for micellar self-assembly of copolymers.^{33,89} The formed micelles can be divided into three categories based on the different components: 1) two oppositely charged block copolymers,⁹⁰ and 2) block copolymer and low molecular weight compound,^{33,91,92} and 3) block copolymer and multivalent metal ion.²⁷ When the pair of agents is dissolved in aqueous phase, the oppositely charged segments are bundled together through the electrostatic interaction, which resulting in the formation of polymeric micelles.⁸⁹

2.2.1. Electrostatic interactions from polyelectrolyte copolymers. The aqueous micelles from polyelectrolyte copolymers are well known as polyion complex (PIC) micelles. As above mentioned, the PIC micelles could be self-assembled from two complementary double-hydrophilic copolymers composed of neutral and charged segments through the electrostatic recognition.⁹³ From 1995, Kataoka and coworkers have prepared a series of PIC micelles, and clearly elucidated the formation process, physicochemical properties, mechanism and application in the realm of pharmaceutical delivery.^{90,93-96} However, the applications of PIC micelles in the delivery of hydrophobic or neutral drugs were obstructed, because they retained a water soluble "stealth" core, *i.e.*, the complexes of polyanions and polycations.

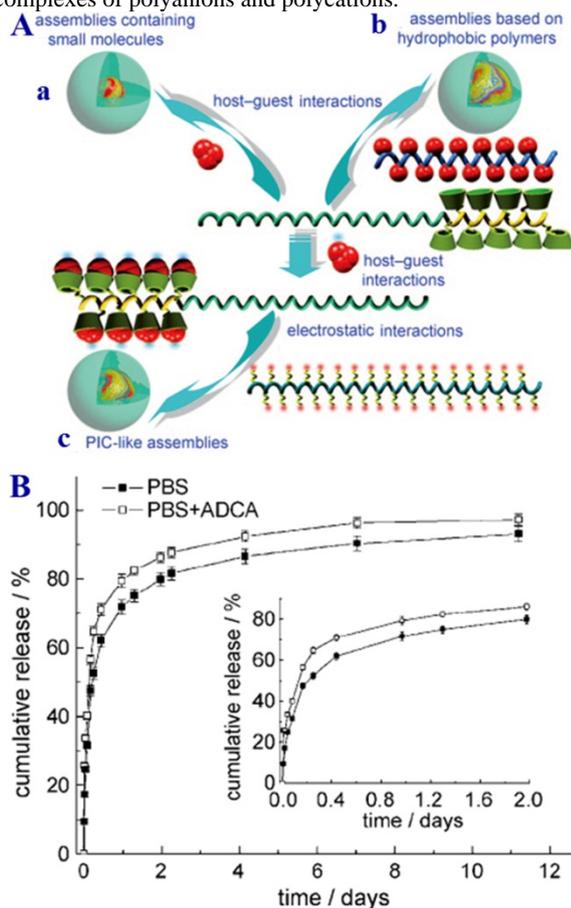


Fig. 7 (A) Schematic illustration of the formation of various supramolecular micelles: (a) hydrophobic molecules mediated self-assemblies, (b) self-assemblies formed with a hydrophobic polymer, and (c) PIC-like self-

assemblies; (B) *in vitro* release profiles of assemblies based on PEG-*b*-PβCD and IND (12.8 wt.%).¹⁰⁹

2.2.2. Electrostatic interactions between polyelectrolyte copolymer and drug. As a supplement, the charged drugs (*e.g.*, DOX) could combine with the oppositely charged polyelectrolyte copolymers, and the obtained amphiphiles subsequently self-organized into micelles for smart drug delivery. For instance, Chen and coworkers prepared the electrostatic interaction-mediated micelles from the amphiphilic complexes between PEG-*b*-PGA or methoxy poly(ethylene glycol)-*block*-poly(γ -propargyl-L-glutamate-*graft*-mercaptopropionic acid) (mPEG-*b*-(PPLG-*g*-MSA)) and DOX.^{97,98} The DOX-loaded micelles with extremely high DLE (almost 100 wt.%) were stable at physiological pH, while rapidly released the payloads at the acidic pH mimicking the endosomal or lysosomal microenvironments. Furthermore, both the obtained DOX-loaded micelles exhibited the enhanced therapeutic efficacy toward A549 lung cancer xenografted nude mice in comparison to free DOX with reduced side effects. In the same group, the polymeric micelles composed of *alkyne*-poly(2-aminoethyl methacrylate)-*graft*-poly(L-glutamic acid) (*alkyne*-PAMA-*g*-PLGA) comb copolymers and DOX were employed to inhibit the proliferation of HeLa cells.¹³ In addition, as shown in Fig. 6, the hepatoma-targeted micelles were prepared from the cooperative self-assembly of galactopeptide and DOX.^{91,92} The fabricated galactose-decorated DOX-loaded micelles enjoyed acidity-accelerated DOX release and improved *in vitro* and *in vivo* antiproliferative capabilities against HepG2 cells compared with that without galactosyl group and free DOX (Fig. 6).

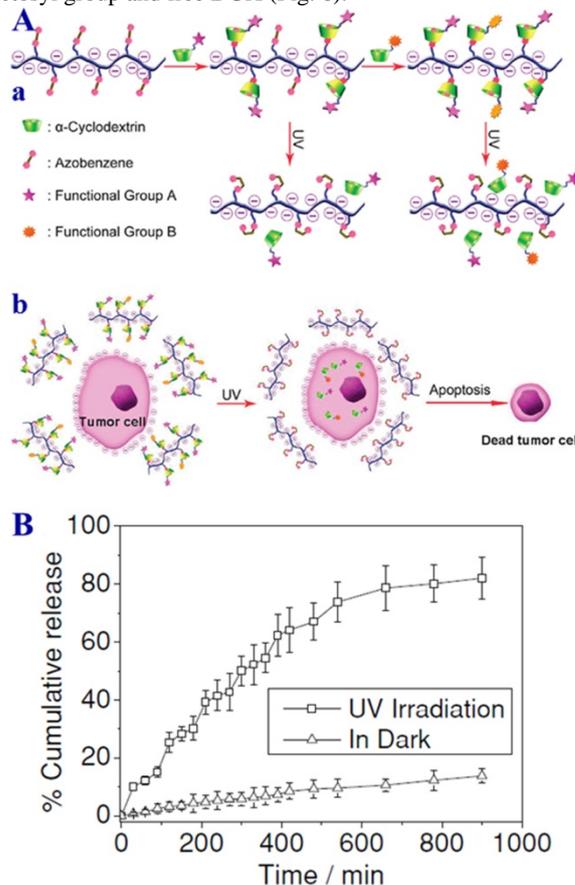


Fig. 8 (A) (a) Schematic illustration of photo-responsive loading and unloading α -CD-modified functional groups toward the polyanionic platform

and (b) the induced apoptosis of tumor cells by uninstal drug driven by UV-irradiation; (B) release behaviors of α -CD-DOX-loaded micelle in dark or under UV-irradiation (365 nm).¹²¹

2.2.3. Electrostatic interactions among polyelectrolyte copolymer and multivalent metal ions. The interactions between the negatively charged polymers and di- or multivalent metal cations as other electrostatic interplays were also exploited to strengthen the polymeric micelles. As a typical example, with a clear mechanism being revealed by Tam *et al.*,⁹⁹ Ahn and coworkers prepared the electrostatic interaction-assisted polymeric micelle with crosslinked ionic interlayer from methoxy poly(ethylene glycol)-*block*-oligo(L-aspartic acid)-*block*-poly(ϵ -caprolactone) and calcium chloride for the delivery of PTX.²⁷ The PTX-loaded stabilized micelle exhibited a slow and sustained release pattern after the burst release at the beginning 10 h, and displayed slower PTX release in the test duration compared with that of the uncrosslinked one.

2.3. Host-guest interactions

Host-guest interactions are one kind of the most commonly used bridges in supramolecular self-assembly.¹⁰⁰ Macrocycles are an essential component for the molecular recognition in the process of

host-guest interaction-mediated self-assembly, which provide the precursors for constructing novel nanoaggregations.¹⁰¹ Cyclodextrins (CDs) are the widely applied macrocyclic molecules as the "host" segments for host-guest combination.^{28,102} CDs are a family of natural cyclic oligosaccharides that are discovered by Villiers in 1891.¹⁰³ The three most common naturally produced CDs, *i.e.*, α -, β - and γ -CDs, are respectively comprised of 6, 7 and 8 D(+)-glucose units with α -1,4-glucosidic linkages, which are obtained from the enzymatic degradation reactions of starches.¹⁰⁴ The rigid and shallow truncated cone-shaped CDs exhibited a hydrophilic exterior and a relatively hydrophobic cavity with a depth of *ca.* 7.8 Å, and the internal diameters are *ca.* 4.5, 7.0 and 8.5 Å for α -, β - and γ -CDs, respectively.¹⁰⁵ The cavities of CDs allow them to spontaneously complex with a variety of guest molecules to form the supramolecular inclusion complexes driven by host-guest interactions, that is, a combination of geometric compatibility, Van der Waals forces and hydrophobic interactions.¹⁰⁶ Recently, several different kinds of supramolecular self-assemblies are fabricated as promising drug delivery systems through inclusion complexations (*i.e.*, host-guest interactions), such as CD-drug composites, multi-component self-assemblies and polymer-CD inclusion complexes.

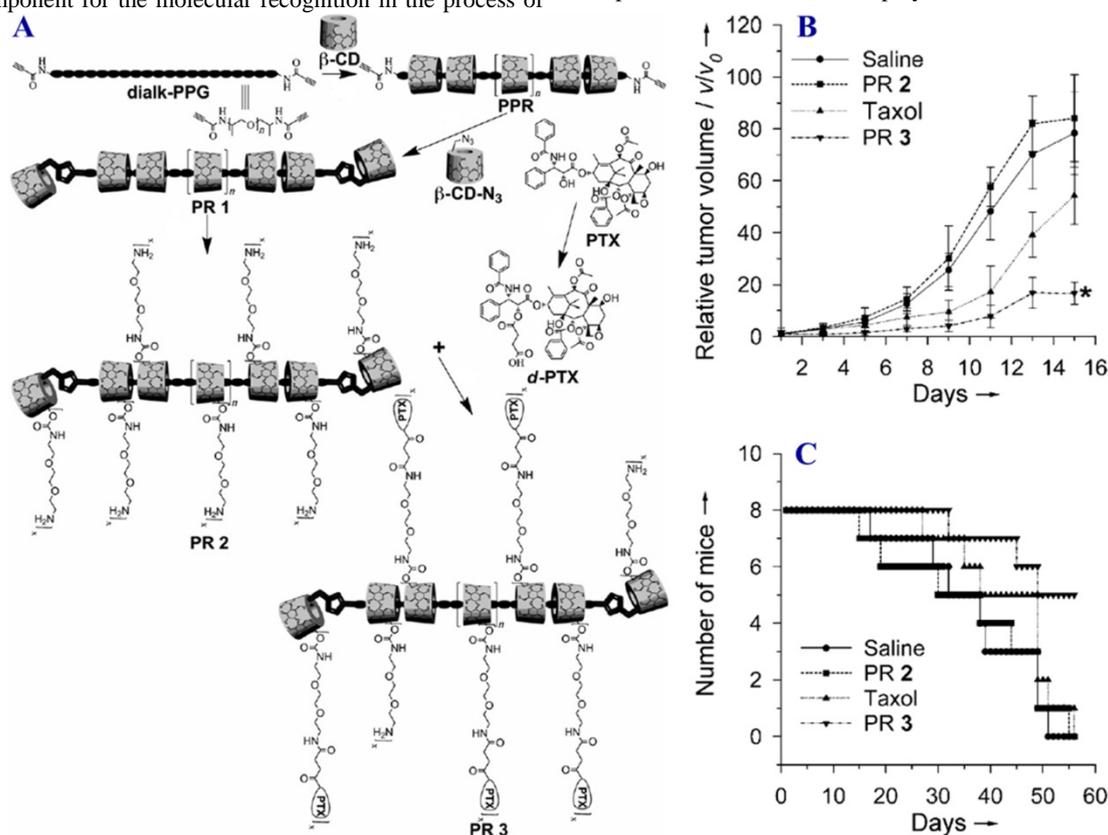


Fig. 9 (A) Synthesis pathways of pseudopolyrotaxane (*i.e.*, PR 2) and pseudopolyrotaxane-PTX prodrug (*i.e.*, PR 3); (B) *in vivo* antitumor efficacy and (C) Kaplan-Meier curves (*i.e.*, survival curves) of H22 xenografted mice treated with different formulations at a dosage of 10 mg PTX per kg body weight through *i.v.* every four days and three time totally (**p* < 0.05 versus Taxol[®]-treated group from days 5).¹²³

2.3.1. Host-guest interactions between CDs and drugs. As aforementioned, the host-guest interactions between CD in polymers and hydrophobic drugs are capable of encapsulating a hydrophobic drug to form drug-loaded micelles in aqueous solution. Caliceti *et al.* synthesized a targetable β -cyclodextrin-poly(ethylene glycol)-folic acid (β -CD-PEG-FA) through condensation reaction for potential hydrophobic drug delivery with rhodamine B (RhB) as a model molecule.¹⁰⁷ Similarly, Sun and coworkers synthesized β -CD-PEG-FA through "click chemistry" strategy for the delivery of 5-fluorouracil (5-FU).¹⁰⁸ The 5-FU-loaded micelle exhibited enhanced

endocytosis and antiproliferative efficacy toward folate receptor (FR)-overexpressing cells (*e.g.*, HeLa cells) compared with the normal ones (*e.g.*, A549 cells). Ma and Zhang synthesized a diblock hydrophilic copolymer composed of PEG and β -CD side-modified polyaspartamide (PEG-*b*-P β CD).¹⁰⁹ As depicted in Fig. 7A, the supramolecular micelles were successfully engineered with the direction of the inclusion interaction between the host PEG-*b*-P β CD and the guest substance, such as, pyrene, adamantane carboxylic acid (ADCA), poly(β -benzyl L-aspartate) (PBLA) and indomethacin (IND). The host-guest mediated systems provided a versatile

platform for the delivery of different hydrophobic drugs benefited from the promising inclusion-solubilization performance of β -CD.¹¹⁰ As shown in Fig. 7B, the payload release (e.g., IND) from the supramolecular micelle could be accelerated by the addition of another hydrophobic molecule with larger association constant (e.g., ADCA). Zhang *et al.* synthesized a β -CD-containing star-shaped copolymer by the atom transfer radical copolymerization of mono- or multi-methacrylate functionalized β -CD and 2-(dimethylamino) ethyl methacrylate with bromine-modified mPEG as macroinitiator.¹¹¹ DOX was entrapped into the polymeric micelle through the host-guest interactions between the β -CD in star-shaped copolymer and favorable hydrophobic agent. The DOX-loaded

micelle exhibited efficient endocytosis and intracellular DOX release, and improved cellular cytotoxicity in comparison to free DOX. Furthermore, Monti and colleagues employed epichlorohydrin crosslinked β -CD-polymer or citric acid crosslinked γ -CD oligomers to encapsulate DOX, and the related mechanisms were studied.^{112,113} Subsequently, Chauhan *et al.* prepared the poly(β -cyclodextrin)/curcumin (CUR) complex micelle for the prostate cancer targeted drug delivery.¹¹⁴ The CUR-loaded micelle presented improved antiproliferative efficacies toward C4-2, DU145 and PC3 prostate cancer cells.

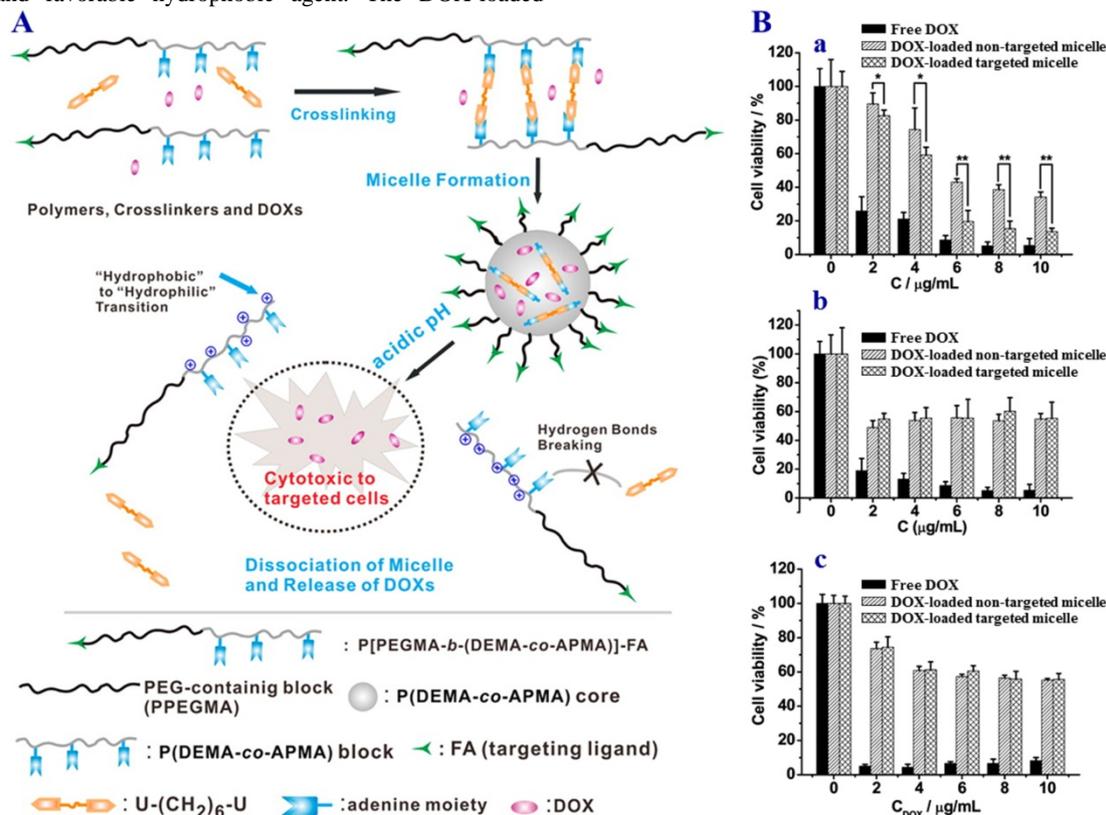


Fig. 10 (A) Schematic illustration for the preparation of DOX-loaded FA-modified multifunctional micelles with nucleobases pairing cross-linked core; (B) cytotoxicities of free DOX, DOX-loaded non-targeted micelle and DOX-loaded targeted micelle toward (a) HeLa (FR+), (b) L929 (FR-) and (c) A549 (FR-) cells after incubation for 48 h (* $p < 0.01$).¹³⁰

2.3.2. Host-guest interactions for multi-component self-assemblies. In addition to encapsulating the hydrophobic drugs, the inclusion complexations between CD and hydrophobic molecules are employed to construct multicomponent assemblies.^{115–118} Many related systems are exploited as intelligent drug nanovehicles.^{119,120} As a typical example, Chen, He and coworkers fabricated the intracellular pH-responsive block amphiphiles composed of benzimidazole (BM)-modified poly(ϵ -caprolactone) (BM-PCL) and β -CD-terminated Dex (Dex- β -CD) through the host-guest interaction.¹¹⁹ DOX was loaded into Dex- β -CD/BM-PCL micelle, and the smart DOX-loaded supramolecular micelles exhibited acidity-triggered payload release and presented high efficacy to inhibit the proliferation of HepG2 cells compared with the unresponsive one. As shown in Fig. 8A, Zhang *et al.* developed a light-responsive "plug and play" polyanionic template consisting of poly(acrylic acid) (PAA) and azobenzene (Azo) for intelligent drug delivery.¹²¹ The α -CD-modified drugs (e.g., α -CD-DOX) and functional groups (e.g., α -CD-RhB and α -CD-lactobionic acid) could be loaded and unloaded driven by the photo-switchable host-guest interaction between α -CD and Azo (Fig. 8Aa). In the current

system, the loaded drug could release from the micelle triggered by the UV-irradiation, and thereby reach desirable therapy effect toward model HeLa cells (Fig. 8Ab and B). Furthermore, the voltage-responsive micelle based on the assembly of PEG- β -CD and ferrocene (Fc)-terminated PLA through the inclusion complexation between β -CD and Fc was exploited by Yuan and coworkers.¹²² PTX was loaded into micelle, and the voltage-triggered PTX release were revealed.

2.3.2. Host-guest interactions of pseudopolyrotaxanes. The pseudopolyrotaxanes constituted by CDs or their derivatives and polymers are another kind of supramolecular polymers as matrices for drug delivery. For example, Gu, He and colleagues prepared the pseudopolyrotaxane micelle from 7-carboxymethoxy coumarin-modified PEG and α -CD for DOX delivery.¹²³ The DOX-loaded micelle exhibited comparable antiproliferative efficacy toward B16 cells (a mouse melanoma cell line) to free DOX. Moreover, the above DOX-loaded micelle showed improved tumor inhibition rate toward 4T1-bearing mice compared with free DOX revealed by Lai, Liu and coworkers. In addition, the pseudopolyrotaxane-PTX or DOX prodrug micelles were reported in recent years.^{124,125} In details,

Jiang and Wu *et al.* prepared the pseudopolyrotaxane–PTX micelle with poly(propylene glycol) as backbone, β -CD as end-capping group and PEG as linker (Fig. 9A).¹²⁴ The prodrug micelle can be internalized readily by tumor cells (*e.g.*, SH-SY5Y (a human neuroblastoma cell line) and H22 cells) and retain the pharmacological activity of PTX. Furthermore, the prodrug platform gave H22 xenografted mice enhanced *in vivo* antitumor efficacy and prolonged survival time (Fig. 9B and C). In addition, Ji *et al.* prepared the stable pseudopolyrotaxane prodrug micelle composed of α -CD-hydrazide-DOX·HCl and poly(ethylene glycol)-*block*-poly(2-methacryloyloxyethyl phosphorylcholine) block copolymer.¹²⁵ The obtained endosomal pH-responsive prodrug micelle could effectively release DOX at pH 5.0 and inhibit the proliferation of tumor cells (*e.g.*, HepG2 cells).

2.4. Hydrogen bonding interactions

Hydrogen bonding interactions are the selective and directional noncovalent interactions, which only form between hydrogen bonding donor and receptor.⁸⁹ The participations of hydrogen bonding interactions direct the self-assembly of copolymers and stabilize the micellar cores, which exhibit great potential as drug nanocarriers.^{126,127} Since 2010, Yang and collaborators reported a series of block copolymers composed of PEG and urea-functionalized polycarbonates, which could form stable micelles enhanced by the presence of hydrogen bonds between urea groups.^{126,128} DOX was more efficiently loaded into urea-containing micelles along with the increased affinity between DOX and hydrophobic micellar cores, and the increase in urea content led to a slight decrease in DOX release rate. The DOX-loaded micelle exhibited effective inhibition toward the proliferation of HepG2 cells. In the same group, the elongated, spherical or disk-like micelles were prepared from the PEGylated amphiphiles with *bis*(thiourea) as interface, and stearyl, oleyl or dodecanol as hydrophobic segments, respectively.¹²⁹ DOX was loaded into micelles mediated by the recognize molecule (*i.e.*, *bis*(thiourea)), and the DOX-loaded micelle presented controlled DOX release and a certain cytotoxicity. In addition, Huang, Meng *et al.* prepared the hydrogen bonding-modulated polymeric micelles composed of amphiphilic methoxy poly(ethylene glycol)-*block*-poly(L-lactide-*co*-2-methyl-2(3-(2,3-dihydroxypropylthio) propyloxycarbonyl)-propylene carbonate (MAC)/1-carboxymethylthymine) (mPEG-*b*-P(LA-*co*-MPT)) and 9-hexadecyladenine for pH-responsive DOX delivery.¹²⁷ The DOX-loaded micelles exerted comparable cytotoxicities against MDA-MB-231 cells, which were just a little lower than free DOX. Furthermore, as shown in Fig. 10, the hydrogen bonding interaction was exploited as crosslinking point in the core of micelle.^{130,131} In Huang and Meng's group, nucleobases (adenine (A) and thymine (T)) were conjugated to the amphiphilic mPEG-*b*-P(LA-*co*-MAC), and the reinforced polymeric micelles were fabricated through the core-crosslinking with the hydrogen bonds between A and T.¹³⁰ DOX was encapsulated into the micelles, and the DOX-loaded micelles exhibited acidity-accelerated payload release. The micelles with DOX showed efficient endocytosis and similar antitumor efficacies as free DOX against MDA-MB-231 cells. In addition, Zeng, Wu and coworkers prepared the targeted and pH-responsive nanocarriers from the folic acid and a functionalized amphiphilic polyacrylate block copolymer and 1,1'-(hexane-1,6-diyl)*bis*(uracil) for smart antitumor drug delivery (*e.g.*, DOX).¹³¹ Under neutral pH, the DOX-loaded micelles enhanced by the complementary multiple hydrogen bonding were stable with diameter of around 170 nm in aqueous solution, and dissociated at acidic pH and rapidly release the payload. Moreover, the DOX-loaded multifunctional micelles exhibited preferable internalization and antiproliferative capability toward FR-positive tumor cells (*e.g.*, HeLa cells) compared with the negative

cells (*e.g.*, L929 (a mouse fibroblast cell line) and A549 cells).

2.5. Stereocomplex interactions

Molecular chirality is a one kind of the important natural properties, which affects the physiochemical properties and biological activities.^{132,133} As a downstream derivative, the polymeric stereocomplexations are defined as the stereoselective interactions between two complementary stereoregular (co)polymers, which result in a new polymeric composite with the improved characteristics compared with the parent (co)polymers, such as enhanced thermal and mechanical resistance, enhanced stability and reduced degradation rate.^{134–139} The above-reported advantages lend the polymeric stereocomplexes to great potential applications as biomaterials, especially in the realm of drug delivery.^{140–142} With regard to drug delivery, the stereocomplex interaction-assisted polymeric micelles attract gradually increasing attention in recent years, and the complementary isotactic and syndiotactic PLAs and amino acid-containing polymers are the most promising polymeric matrices attributed to their good biocompatibility.^{30,142,143}

2.5.1. Stereocomplex interactions of enantiomeric polyesters. Since Ikada *et al.* first reported the stereocomplexation of poly(L-(–)-*S*-lactide) (PLLA) and poly(D-(+)-*R*-lactide) (PDLA) in both the melt and solution in 1987, many continued works have been performed including their systematic preparation and characterization.^{144,145} The stereocomplex micelles (SCMs) from the enantiomeric PEG–PLA copolymers were the initially researched systems, which were employed for the possible clinical delivery of therapeutic cargos thanks to the biocompatible FDA-approved compositions.⁸⁹ More interestingly, the stereocomplex PEG–PLA micelles exhibited a partially microcrystalline and more compact hydrophobic core in comparison to that of the individual enantiomers.¹⁴² Based on the above merits, Chen *et al.* employed the SCMs for the sequestration and controlled release of rifampin in 2007.¹⁴⁶ Subsequently, Li and coworkers in-depth studied the self-assembly behaviors and extended the above micelle as the nanocarrier of PTX.^{147,148} The PTX-loaded SCMs prepared by both direct dissolution and dialysis methods exhibited improved DLEs compared with that of PTX-loaded individual micelles. The PTX-loaded micelles derived from direct dissolution presented faster PTX release than those from dialysis. Moreover, the PTX-loaded micelles could keep PTX at high concentrations in different tissues after intraperitoneal injections, and exhibited extended half-life in circulatory system and enhanced antitumor abilities compared with clinical formulation. Hedrick, Yang and coworkers synthesized the Y-shaped PEG–(PLLA)₂, PEG–(PDLA)₂ and PEG–PLLA–PDLA copolymers, and the PTX-loaded stereoregular PEG–(PDLA)₂ micelle, and autologous and allogeneic SCMs were prepared.¹⁴⁹ The DOX-loaded allogeneic SCM exhibited the highest DLE, while the individual one showed the lowest level. Both the two SCMs displayed the comparable sustained and near zero-ordered release of PTX without significant initial burst, which was slightly slower than that of individual micelle. In addition, the biodegradable SCMs originated from amphiphilic Dex-*b*-PLA were prepared for the controlled DOX delivery in Chen and He's group.¹⁵⁰ The DOX-loaded SCMs exhibited slower extracellular and intracellular DOX release, which resulted in the relatively lower antiproliferative activities toward HepG2 cells. Recently, He, Gu and colleagues prepared the pH-responsive SCM based on methoxy poly(ethylene glycol)-*block*-poly(L-histidine)-*block*-poly(lactide) (mPEG-*b*-PH-*b*-PLA) triblock copolymers as potential intelligent drug nanocarriers.¹⁵¹

2.5.2. Stereocomplex interactions from chiral amino acid-containing (co)polymers. The amino acid-containing (co)polymers are another kind of potential matrices for constructing SCMs. For

example, O'Reilly and collaborators reported the syntheses of enantiomeric (co)polymers with polyacrylate or polyester as backbones, and the L-leucine and D-leucine derivatives as side groups.^{152–155} The different self-assembly behaviors of individual or enantiomeric (co)polymers were revealed, and the results indicated the great potentials in drug delivery. In addition, the complementary

stereoregular polypeptides with amino acid units in the backbone could also be employed as matrices for fabricating SCMs, and certain preliminary tentative works were launched.³⁰ Although still in their infancy, the SCMs derived from the amino acid-containing (co)polymers displayed bright prospect as controlled drug delivery platforms.

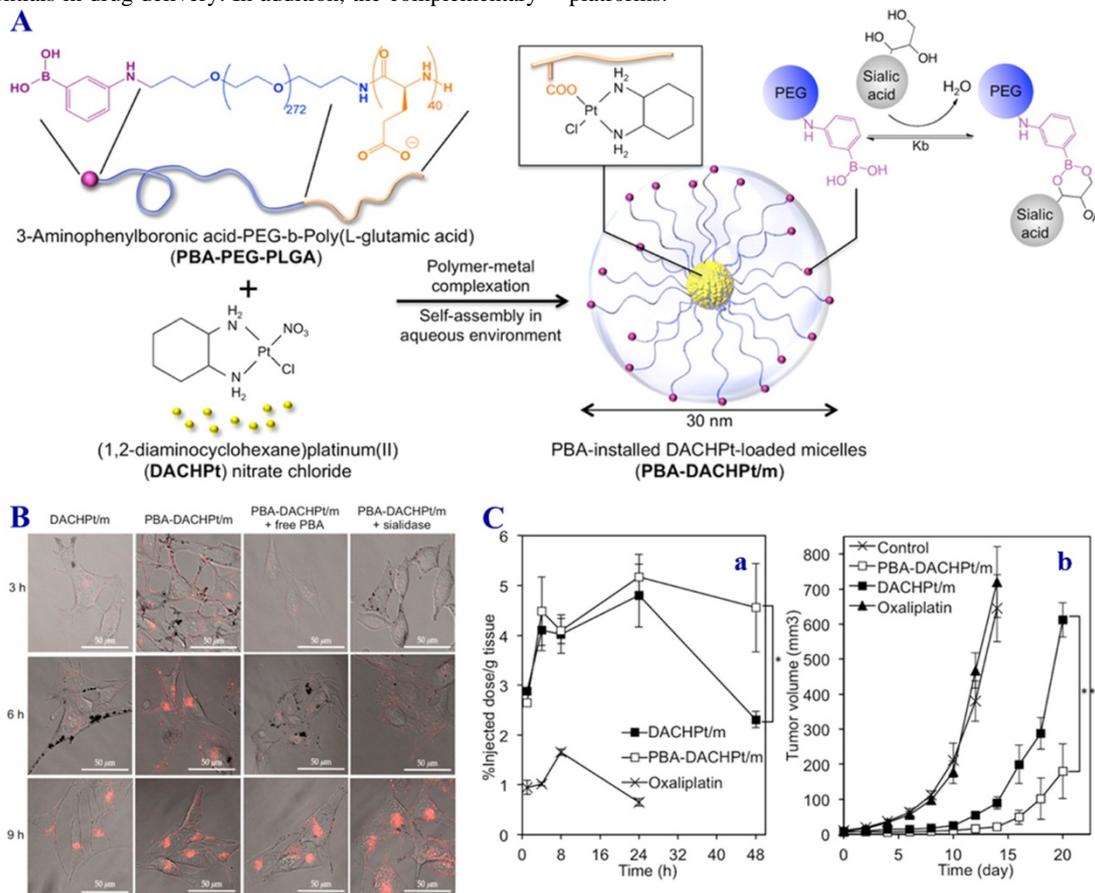


Fig. 11 (A) Schematic illustration for the preparation of PBA-decorated DACHPt-loaded micelle (*i.e.*, PBA-DACHPt/m) through polymer-metal complex formation between DACHPt and PBA-PEG-*b*-PLGA in distilled water. PBA moieties on the surface of micelles can bind to SA. (B) Fluorescent microimages of B16F10 cells incubated with Alexa Fluor 555-labeled DACHPt/m or PBA-DACHPt/m after incubation for 3, 6 and 9 h. Free PBA was added or the cells were pretreated with sialidase before the addition of PBA-DACHPt/m for the comparative assays. (C) (a) tumor accumulation of DACHPt/m and PBA-DACHPt/m in mice models bearing B16F10 tumors; (b) antitumor activity against orthotopic B16F10 tumors after treatment with DACHPt/m, PBA-DACHPt/m (3 mg/kg) or oxaliplatin (8 mg/kg) injected on days 0, 2, and 4. Data are means \pm standard error of the mean, $n = 5$, $*p < 0.05$, $***p < 0.001$.

2.6. Coordination interactions

Organometallic coordination interactions are another kind of noncovalent interactions used for improving the polymeric micelles. Platinum(II) (Pt(II))-containing organometallic complexes, such as cisplatin (CDDP) and (1,2-diaminocyclohexane)platinum(II) (DACHPt), are the commonly used complex and pharmaceutical active agents.^{156,157} Since 1996, Yokoyama, Nishiyama, Kataoka and collaborators have incorporated CDDP into polymeric micelles of diverse scales in the range of 20 – 100 nm with poly(ethylene glycol)-*block*-polypeptide copolymers as matrices by ligand substitution reaction, in which PEG served as outer shell and CDDP-incorporated polypeptides constituted inner core.^{158–163} CDDP-combined polymeric micelles that prepared *via* polymer-metal complex formation showed tunable sustained release profiles with the concentration change of sodium chloride and delayed blood clearance.^{159,160,163} The subsequent preclinical studies revealed that the nanovehicles were preferentially distributed to tumors by enhanced permeability and retention effect, and exhibited significantly lower toxicities and greater antitumor activities toward

various solid tumors (*e.g.*, colonic, gastric, lung and breast cancers) compared with free CDDP.^{160,162–166} On the basis of the achieved favorable results, the CDDP-integrated PEG-*b*-PLGA micelles (trade name: NC-6004) were pushed to clinical trials, and now the formulations are ongoing phase III clinical trials in Taiwan and Singapore.¹⁵⁶ As a follow-up development, DACHPt (*i.e.*, an active parent complex of oxaliplatin) is also employed to strengthen the micelles and serve as an active agent. Kataoka and collaborators prepared a series of DACHPt-incorporated mPEG-*b*-PLGA micelles with various diameters from 30 to 100 nm through adjusting the compositions of copolymers and the content of DACHPt.^{31,157} All the DACHPt-loaded micelles could penetrate the highly permeable tumors (*e.g.*, C26 mouse colon adenocarcinoma), but only the 30 nm micelle could penetrate poorly permeable tumors (*e.g.*, BxPC3 human pancreatic cancer) to obtain an efficient antitumor effect.¹⁵⁷ Fortunately, the penetrations of larger micelles could be enhanced by the presence of a transforming growth factor- β inhibitor that could improve the permeability of tumors.^{157,167} The DACHPt-integrated micelle of 30 nm demonstrated the improved inhibition efficacy against spontaneous mouse pancreatic tumor with prolonged survival and prevented peritoneal metastasis.³¹ As shown in Fig. 11, mediated

by the overexpressed sialylated glycans receptor (*i.e.*, sialic acid, SA) in tumor cells, the phenylboronic acid (PBA)-installed platform with DACHPt (29 nm) exhibited enhanced therapeutic effects toward B16F10 mouse melanoma accompanied by reduced plasma clearance, enhanced accumulation in tumor tissue and endocytosis, and inhibited lung metastasis.¹⁶⁸ Moreover, the cyclo(Arg-Gly-Asp-D-Phe-Lys) (c(RGDfK))-modified CDDP-combined micelle displayed highly efficient drug delivery and inhibition efficacy to U87MG intractable human glioblastoma benefited from the

specific recognition on $\alpha_v\beta_3/\alpha_v\beta_5$ integrins, which are overexpressed in angiogenic sites and tumors.¹⁶⁹ In addition, Jing *et al.* incorporated DACHPt to the amphiphilic block copolymers composed of PEG and mono- or dicarboxyl functional polycarbonates.^{170,171} The DACHPt-loaded micelles exhibited acidity-accelerated release profiles and enhanced or comparable antiproliferative efficacies toward a variety of tumor cells (*e.g.*, SKOV-3, MCF-7 or HeLa cells).

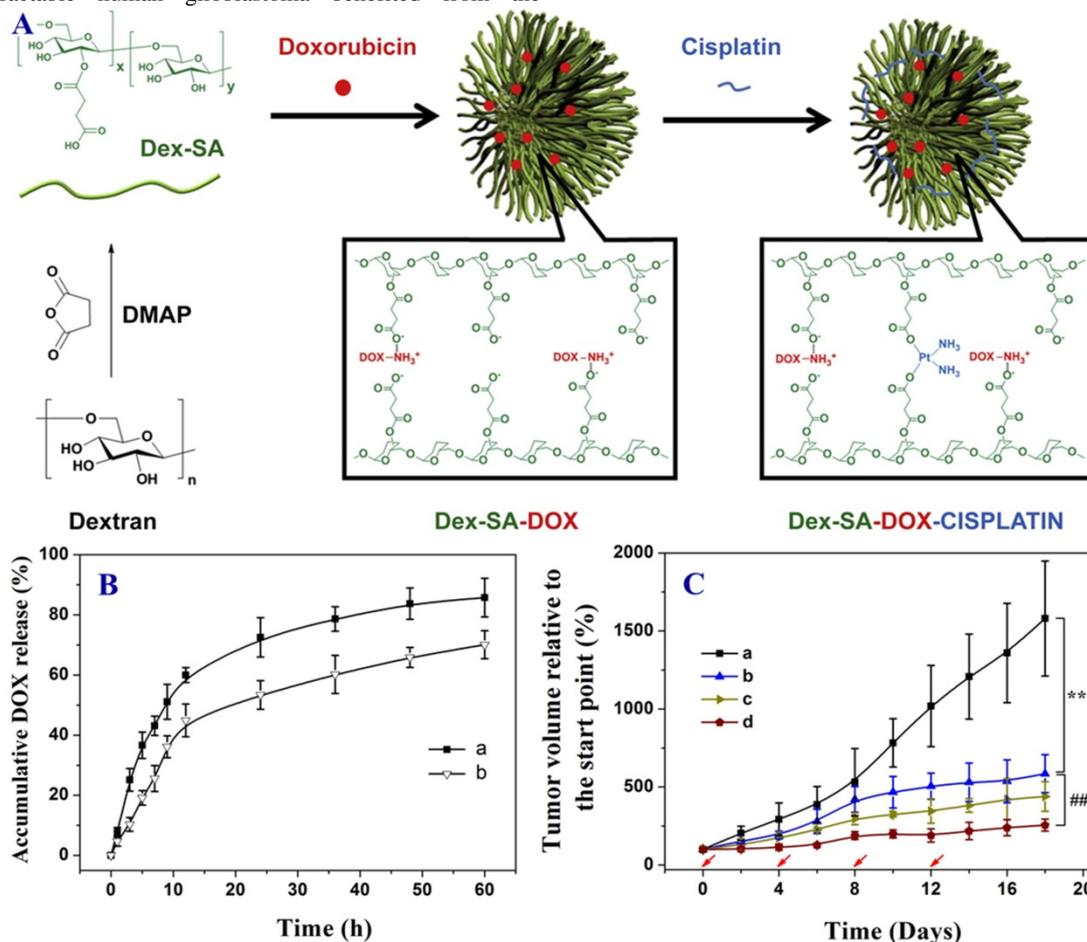


Fig. 12 (A) Schematic illustration for the preparation of DOX-loaded CDDP-integrated micelle; (B) (a) DOX release profiles of DOX-loaded micelle and (b) DOX-loaded CDDP-incorporated micelle in PBS at 5.5; (C) *in vivo* tumor sizes of the mice as a function of time after the *i.v.* treatments with (a) PBS, (b) free DOX (3.0 mg kg^{-1}), (c) DOX-loaded micelle (3.0 mg kg^{-1}) and (d) DOX loaded CDDP-incorporated micelle (3.0 mg kg^{-1} DOX) in the A549 tumor bearing mice model ($^{##}p < 0.01$, $^{***}p < 0.001$). The arrows represented the *i.v.* days.³²

2.7. Multiple interactions

In addition to the above-described individual weak interactions, many other fascinating synergistic forces composed of two or more noncovalent interactions are also employed to stabilize the micelles and simultaneously assigned the micelles a certain intelligences and biological activities. Chen, Liu and coworkers prepared the DOX-loaded micelles based on poly(ethylene glycol)-*block*-poly(L-glutamic acid-*co*-L-phenylalanine) (mPEG-*b*-P(LGA-*co*-LP) through the combination of π - π stacking and electrostatic interactions.¹⁷² The DOX-loaded micelle exhibited a high DLE ($\sim 98 \text{ wt.}\%$), a pH-responsive release profile, an increased MTD and an enhanced antitumor activity toward the model of A549 xenografted nude mice with reduced side effects. Taking advantage of π - π stacking and coordination interactions, Tang *et al.* codelivered PTX and CDDP with mPEG-*b*-PGA-*b*-PLP micelle.¹⁷³ The PTX/CDDP-loaded micelle displayed sustained PTX and CDDP release, and a

high synergism effect in the inhibition of A549 human lung cancer *in vitro* and *in vivo*. With the same driving forces, Tang and colleagues subsequently conjugated VE and PEG to PGA backbone to construct a polypeptide-based micellar platform for the codelivery of docetaxel and CDDP, and an $\alpha_v\beta_3$ integrin targeting peptide (that is, c(RGDfK)) was further decorated on the surface of micelle.¹⁷⁴ The targeting dual drug-loaded micelle exhibited remarkable synergistic cytotoxicity toward B16F1 cells *in vitro* and *in vivo*, and showed enhanced antimetastasis efficacy against B16F10 cells *in vivo*.

Yang and collaborators prepared the DOX-loaded micelles based on a series of block copolymers composed of PEG and the carboxyl and urea dual-functionalized polycarbonates through the synergistic electrostatic and hydrogen bonding interactions.^{29,175} The DOX-loaded micelles exhibited sustained DOX release, and slightly reduced or comparable cytotoxicities toward HepG2 cells. Chen, Zhang and coworkers prepared the DOX and CDDP loaded micelles with succinic acid-decorated Dex as backbone through the combined

forces of electrostatic and coordination interactions.³² The DOX-loaded CDDP-integrated micelles exhibited an acidity-accelerated DOX release, and improved pharmacokinetics, biodistribution, MTD and antitumor efficacy against A549-bearing nude mice model (Fig. 12). In addition, Bronich and coworkers prepared the electrostatic and coordination interactions-assisted polymeric micelles with crosslinked ionic cores from poly(ethylene glycol)-*block*-poly(methacrylic acid) and calcium chloride for the delivery of CDDP.¹⁷⁶ The CDDP-loaded micelle released CDDP in a sustained manner in physiological saline and exhibited efficient cisplatin internalization and antiproliferative activity toward A2780 cells (a human ovarian carcinoma cell).

3. Conclusions and outlooks

In the past few decades, various individual noncovalent interactions (e.g., strong hydrophobic, electrostatic, host-guest, stereocomplex and coordination interactions) or their synergistic associations were employed to facilitate the micelles or endow them with the additional intelligences or bioactivities. As one kind of blooming upgraded nanovehicles, the noncovalent interaction-assisted polymeric micelles exhibited the amazing potential of the applications in the realm of controlled drug delivery, and certain species are ongoing clinical trials of various phases.

Although the weak interaction-mediated polymeric micellar nanocarriers exhibit fascinating perspectives, the designs, preparations and applications of the emerging systems are still in their initial statuses and there is a broad space for their development. First, in order to facilitate the clinical practices, the polymeric micelles need to be developed on the basis of hydrophilic or amphiphilic (co)polymers with appropriate biocompatibility and biodegradability. Second, some other promising interactions should be introduced from the prosperous supramolecular chemistry or self-assembly to enrich the tool library for the micellar upgrade or replacement. Third, the improved polymeric micelles of functional integration including stimuli-responsiveness, targetability, detectability, and so on, for promising theranoses of severe illnesses should be specially focused on, given that it is relatively difficult for the traditional micelles. Forth, intelligence is another trend for the updated micelles, which keep stable in the circulatory system, undergo rapid dissociation at the desired lesion sites for drug release and eventually can be completely metabolized by the organisms. Fifth, in view of the weak and reversible interactions, and the complicated microenvironments, the *in vivo* efficacies and securities should be systematically preassessed for potential applications. With the sustained endeavors in the development of advanced materials, methodologies, versatilities, intelligences and applications, the improved noncovalent-assisted polymeric micelles are expected to play a more important role in controlled drug delivery.

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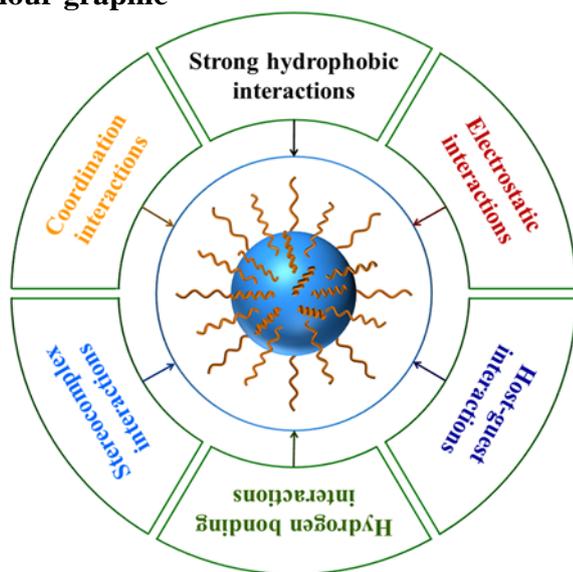
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Colour graphic**Text**

Various individual or synergistic noncovalent interactions were employed to mediate polymeric micelles for controlled drug delivery.

Photographs and biographies



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Xiuli Zhuang has been a professor in CIAC, CAS since 2011. She graduated from CIAC, CAS and received her MS degree in 1994, and obtained her PhD degree in Waseda University, Japan, in 2010. Up to now, she has published more than 100 pre-reviewed research papers in academic journals. In addition, she has applied over 100 Chinese patents, of which more than 40 ones were authorized. Recently, her research focuses on the development of 1) industrializations of biodegradable polymers (*e.g.*, polylactide, poly(lactide-*co*-glycolide) and polypeptides); 2) stimuli-responsive biodegradable polymers as drug carriers; 3) smart nanoscale platforms for targeting drug delivery.

**Xuesi Chen**

Xuesi Chen received his PhD degree at Waseda University, Japan, in 1997, and completed his post-doctoral fellowship at the University of Pennsylvania, USA, in 1999. He has been a full Professor at CIAC, CAS since 1999. He has published over 400 articles in academic journals, which have been cited for more than 8,000 times until now. In addition, he has applied over 200 Chinese patents and more than 80 ones have been authorized. His research interests focus on the development and biomedical applications of biodegradable polymers, mainly focused on polyethers, polyesters, polypeptides, polycarbonates and their copolymers.