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Cyclodextrin-functionalized Polymers as Drug Carriers for Cancer Therapy

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Abstract:

Cyclodextrins (CDs) represent the most extensively investigated cyclic molecules due to their wide availability, facile functionalization, unique amphiphilicity and inclusion capacity. The marriage of CD chemistry with polymer science has generated novel biomaterials by integrating supermolecular host-guest chemistry and state-of-the-art polymer chemistry techniques. The current mini-review focuses on the recent progress on CD-functionalized polymers as drug carriers for cancer therapy. CD-functionalized polymers with different structures are summarized. Their application as drug carriers for cancer therapy is then highlighted. At the end, the future directions of this rapidly developing research field are discussed.

Keywords: Cyclodextrin; host-guest chemistry; polymer chemistry; drug delivery; cancer therapy

1. Introduction

Cyclodextrins (CDs) are a family of cyclic oligosaccharides comprised of α-(1→4)-linked D-glucopyranoside units that are readily acquired from starch via a simple enzymatic conversion.[1] Since their discovery by Villiers in 1891,[2] CDs have drawn extensive attention from various research fields due to their wide availability, facile functionalization and low immunogenicity[3], thus making them ideal candidates for a broad range of applications as well as industrial manufacture.

α-, β- and γ-CDs are the common members in CD family, and contain six, seven and eight glucopyranose units, respectively. They are all generally recognized as safe by the FDA, and show a truncated cone architecture with both primary (narrow side) and secondary (wider entrance) faces (**Figure 1**).[4-6] Due to the presence of bristling multi-hydroxyl groups on both faces of the 3D restricted toroid, CDs show a highly polar outer surface with hydrophilicity. On the other hand, the ether-like oxygens and the hydrocarbon frame of CDs confer a non-polar interior cavity with hydrophobicity.[7] CD's unique hydrophobic cavity with specific dimensions[7] offer them inclusion capacity for a variety of guest molecules to fabricate supermolecular inclusion complexes.[8,9]

Figure 1

The rapid advances in state-of-the-art polymer chemistry techniques,[10] such as atom transfer radical polymerization (ATRP)[11] and reversible addition−fragmentation chain transfer (RAFT)[12] polymerization, have witnessed the synthesis of well-defined and relatively uniform polymers with multi-functionalities.

The marriage of CD chemistry with polymer chemistry has enabled the successful engineering of advanced biomaterials with superior properties.[13] This mini-review highlights the recent progress in the construction of CD-functionalized polymers as drug carriers for cancer therapy. A perspective on the future direction of this rapidly developing research field is presented at the end.

2. CD-functionalized polymers

Due to the presence of molecular-compatible cavities and multi hydroxyl groups on the primary face of CDs, CDs can be employed as a building block or junction for the fabrication of polymers either by host-guest interaction or by covalent linkage. In this section, a comprehensive review of the possibilities is given.

2.1 Polymers with CD-embedded backbone

2.1.1 Polyrotaxanes formed by non-covalent link

CD-based polyrotaxanes or pseudopolyrotaxanes (CDPRs), also termed as "molecular necklaces", are a family of supramolecular polymers with CDs threading onto the polymer backbone.[14,15] The Harada's group reported the pioneer work regarding the inclusion complexation of α-CD with poly(ethylene glycol) (PEG) to form crystalline complexes.[16] PEG chains were found to penetrate the CD cavities, and hydrogen bonding was determined to be the primary driving force for this inclusion complex formation.[16] Since the first discovery, there has been increasing interest in fabricating CDPRs by threading CDs onto a polymeric backbone. Subsequent end-capping of the polymer using large terminal groups can trap the threaded CDs, thus maintaining the integrity of CDPRs.[14,15]

Among CDPRs, CDs-PEG systems are extremely attractive for engineering novel biomaterials for controlled drug delivery applications given the excellent biocompatibility of CDs and PEG, as well as the facile decoration of CDs for multi-functionalities. The incorporation of CD units onto the polymer backbone provides plenty of hydroxyl groups along the main chain, thus affording potential multi-conjugation sites for various bioactive agents, such as drug, protein, peptide, antibody, and nucleic acid.

Similar to the core-shell micelles self-assembled from amphiphilic copolymers, the incorporation of amphiphilic CDs onto polymer can alter the amphiphilicity of the overall polymer, resulting in the formation of supramolecular nanoparticles generated by self-assembly of polyrotaxanes.[17] The hydrophobic core of the nanoparticles can encapsulate lipophilic drug physically for controlled release. For example, the groups of He and Gu reported the preparation of polyrotaxanes using

cinnamic-acid-terminated PEG and α-CDs. Interestingly, the morphology of the polyrotaxane-based self-assemblies shifted from vesicle to micelle due to the loading of anticancer drug, doxorubicin (Dox). The Dox-loaded micelles could inhibit the proliferation of 4T1 breast cancer cells efficiently, and their *in vitro* antitumor efficiency was comparable to that of free Dox. Evaluation in a mouse model of breast cancer indicated that the tumor inhibition rate of Dox-loaded polyrotaxanes nanoparticles delivered by intravenous injection was 53%, better than that of free drug. More importantly, the cardiac toxicity of Dox was decreased significantly using the formulation of polyrotaxane-based supermolecular nanoparticles compared to free Dox, demonstrating their great potential for cancer therapy. [18]

In addition to drug loading in polyrotaxanes by physical entrapment via hydrophobic interactions, drugs can be conjugated to the backbone of polyrotaxanes via stimulus-responsive links (e.g., pH- or reduction-responsive bond) that are stable in blood plasma (physiological pH and mildly oxidizing extracellular milieu) yet preferentially cleavable in neoplastic tissues (mildly acidic pH and reductive environment). This prodrug strategy provides a powerful means for drug modification and represents a better approach for the construction of polymer therapeutics because the drug molecules are covalently connected to the polymer main chain, the conjugates are still amphiphilic and can self-assemble into core–shell micelles in which lipophilic drugs exist inside the micellar cores. These micelles not only possess all merits of classic physically entrapped-drug micelles, but also exhibit additional advantages, *i.e.*, polymeric prodrugs exhibit superior protection for drug molecules using covalent links. Such enhanced stability for drug molecules completely eliminates inevitable leakage and premature release of loaded drugs occurring from conventional micelles upon intravenous administration owing to diffusion and dynamic instability, they permit precise tailoring of drug pharmacokinetics *in vivo*. In other words, polymeric prodrugs can improve the *in vivo* drug efficacy as well as reduce drug-associated side effects.[19]

Ji et al. developed pseudopolyrotaxane prodrug micelles with high drug loading content by simply mixing two hydrophilic segments, α-CD-hydrazide-Dox·HCl and

PEG-*b*-poly(2-methacryloyloxyethyl phosphorylcholine) (PEG-*b*-PMPC) block copolymer, in an aqueous solution (**Figure 2**). Since Dox was conjugated to CD rings by an acid-labile hydrazone bond, endosomal pH-triggered drug release was observed. Effective internalization by HepG2 cells and subsequent proliferation of cells were demonstrated using these supermolecular prodrug micelles.[20]

Figure 2

The Caruso group developed degradable capsules composed of cross-linked α-CD/PEG polyrotaxanes with alkyne groups on the outer surface, prepared using silica particles as the sacrificing templates. The assembled CDPRs were then cross-linked using cystamine as a degradable linker, and the surface of the cross-linked CDPRs capsules was further functionalized with clickable PEG moieties. Covalent conjugation of Dox to the hydroxyl groups of the threaded α-CDs afforded Dox-loaded capsules, and the glutathione (GSH)-induced cleavage of the disulfide bonds present in the capsules led to the release of α-CD-DOX conjugates via dethreading. This study shows that the combination of tunable CDPRs with click chemistry for post-functionalization enables the preparation of capsules that are finely tuned with respect to their structure, composition, and functionality, thus making CDPRs-based materials promising drug delivery systems.[21]

Paclitaxel (PTX) is another important antineoplastic agent, and has been shown to exhibit high activity against various solid tumors.[22] Recently, the group of Wu and Jiang synthesized novel CDPRs with dialk-poly(propylene glycol) (PPG) as axle and β-CD-N_3 as end-capping group, in which about 11 β-CD molecules were locked on one axle. A succinate-based PTX ester derivative was covalently attached via a hydrophilic spacer to the hydroxyl groups on the CDPRs (**Figure 3**). The supermolecular CDPR-PTX conjugates showed a desirable drug loading content of ~ 29% and the PTX release can be accelerated by esterase catalysis. The CDPR-PTX conjugates can be internalized readily by a human neuroblastoma (SH-SY5Y) cell line, and retained the pharmacological activity of PTX. The half-life of the ^{99m}Tc-labeled CDPRs in blood circulation, determined by gamma scintillation

counting, is around 5.8 h, much longer than that reported for Taxol (18.8±1.5 min). The evaluation of *in vivo* antitumor performance of CDPRs by using subcutaneous hepatic H22 tumor-bearing mice showed that the resulting CDPRs had a much better tumor suppression effect than Taxol with an equivalent dosage of PTX, that is, 78.7 % tumor growth inhibition for CDPRs VS 30.7 % for Taxol on the 15th day p.i., as well as a much longer median survival time for tumor-bearing mice than all the other formulations-treated groups. The overall results demonstrated great potential of such CDPRs for clinical applications.[23]

Figure 3

2.1.2 Polymers with covalent linked CD in the backbone

Generation of polymers with covalent linked CD in the backbone and their application for drug and gene delivery were pioneered by the group of Mark E. Davis.[24,25] They created a new library of CD-based polymers specifically designed to deliver therapeutics for cancer therapy (**Figure 4**). Linear, high molecular weight *β*-CD-embedded polymers containing alternating *β*-CD units with pendant carboxylic functionalities were prepared based on the polycondensation of a diamino acid derivative of *β*-CD with difunctionalized PEG comonomers. These polymers are all highly soluble in aqueous solutions with low cytotoxicity to cultured cells. Camptothecin (CPT), with very high potency and promising anti-cancer activity against a wide range of cancer cells, was modified and conjugated to the *β*-CD-embedded polymers to generate CD-polymer-CPT prodrugs. The resulting prodrugs displayed significantly enhanced solubility of CPT by more than three orders of magnitude. The antitumor activity of these CD-polymer-CPT conjugates was further investigated in nude mice bearing human LS174T colon carcinoma tumors. The effects of polymer molecular weight (MW), drug loading content, and linkage type on toxicity and tumor growth inhibition were studied in detail. All the CD-polymer-CPT conjugates demonstrated excellent antitumor activity *in vivo*. Notably, the high-MW conjugates produced greater antitumor activity than CPT at the same dose and irinotecan (a FDA-approved small-molecule CPT analog, Camptosar®,

Pfizer) given at a dose approximately 1 order of magnitude higher than those of the conjugates. Their milestone work has established that CD-based polymer is a highly versatile platform that confers significant biological advantages to active pharmaceutical ingredients, including target-tissue localization, enhanced cellular uptake, and slow drug release kinetics, all resulting in sustained therapeutic drug concentrations in target cells. Together, these biological properties provide a strong potential to a bench-to-bedside translation with significant impact on clinical outcomes.[26]

Figure 4

2.2 CD-centered/bridged polymers

CDs' well-defined cyclic structure with fixed numbers of multi-hydroxyl groups has enabled the synthesis of CD-centered star polymers via core-first approach by controlled living polymerization techniques, such as ring opening polymerization (ROP), ATRP, RAFT polymerization, and nitroxide mediated polymerization (NMP).[27] For example, tosylated *β*-CD was explored as initiator by Adeli and co-workers for step by step ROP of lactide and 2-ethyl-2-oxazoline, resulting in the formation of amphiphilic copolymers composed of a CD core, poly(lactide) and poly(oxazoline) arms as nanocarriers.[28] Zhu et al. developed novel well-defined drug-grafted seven-arm amphiphilic star poly(ε-caprolactone-*co*-carbonate)-*b*-PEG copolymers based on a *β*-CD core by the combination of ROP, esterification coupling reactions and ''click'' reactions.[29] The application of thiol-based click chemistry further opens new avenues for CD modification. The group of Becer and Haddleton recently reported the synthesis of CD-centered star polymers via thiol-ene addition of per-6-thio-*β*-CD (CD-$(SH)_7$) with various vinyl terminated polymers. The obtained thiol-ene polymer could be further exploited as an initiator for ROP of ε-caprolactone (ε-CL) to generate different macromolecular architectures with a CD junction.[27] However, the application of these CD-centered polymers as drug delivery systems remains to be explored.

In addition to the CD-centered star polymer, another interesting macromolecular

architecture is CD-bridged polymer formed by CD-guest inclusion complexation. The inclusion complexation between CDs and various guest molecules has been investigated extensively in supramolecular chemistry, covering a broad range of guests, such as small molecules[30], ions[31], proteins[32], and oligonucleotides[33], with an appropriate size. A preceding survey of literature shows that the equilibrium binding constant for the simplest inclusion complexes based on one of the three native CDs (α-, β- and γ-CDs) and various guest molecules at equivalent molar ranges from 1 to 10^6 M^{-1} with a population mean of 10^2 to 10^3 M^{-1}.[34] When the binding ability of a host-guest pair is strong enough, it can be employed to link two polymers with respective host and guest groups at the chain terminals into a pseudo block copolymer with a CD-guest bridge. β-CD and adamantane (AD), as the most extensively investigated pair with a strong binding constant around 1×10^5 M^{-1} in water,[17] has been widely used in polymer fabrication. Barner-Kowollik's group, for example, constructed a series of novel polymer architectures including three-arm[36], miktoarm[37], X- and H-shaped[38] star block copolymers via the combination of state-of-the-art polymer chemistry techniques (RAFT and copper(I)-catalyzed azide–alkyne cycloaddition) and CD-AD driven supermolecular self-assembly.

Zhang and co-workers reported the synthesis of a novel CD-bridged polymer and its application for cancer therapy. The key innovation of their study is the design of an interesting α-β CD dimer, which was used as a junction to bridge the hydrophilic and hydrophobic polymer moieties, wherein a thermo-responsive poly(*N*-isopropylacrylamide-*co*-*N*-acroyloxysuccinimide) (P(NIPAAm-*co*-NAS)) end functionalized with phenyl groups and a hydrophobic poly(ε-caprolactone) (PCL) terminus decorated with AD formed inclusion complexes with α- and β-CDs, respectively. The resulting non-covalently connected block copolymer can self-assemble into core-shell micelles for drug delivery. A peptide containing the Arg-Gly-Asp (RGD) sequence was introduced to the micelles to achieve site-specific internalization. Meanwhile, PEG chains were grafted to the P(NIPAAm-*co*-NAS) backbone *via* tumor acidic pH-responsive benzoic-imine bonds to prevent interaction

of the RGD targeting ligands with normal cells in the circulation of body fluid and in normal tissues, whereas tumor acidic pH-induced removal of PEG chains by the cleavage of such bonds at the tumor sites deshielded RGD sequences to realize targeting towards cancer cells in the vicinity. The Dox-loaded micelles could be internalized by HeLa cells (< pH 6.8), and further release the loaded drug inside tumor cells (> 37 °C) to inhibit the proliferation of cells efficiently.[39]

CD-guest complexation can be expanded facilely to the reversible construction of CD-bridged block copolymers with a CD-guest junction that can be tailored by altering specific properties (e.g. conformation, charge, and solubility) of the guest molecules using an external stimulus, such as pH[40], light[41], and voltage[42]. Such stimuli-responsive self-assemblies are extremely attractive for biomedical applications because this strategy provides one solution to the stability of drug carriers versus efficient drug release dilemma. A recent case in this regard was reported by the groups of He and Chen, in which pH-sensitive host-guest complexation between *β*-CD and benzimidazole (BM) was used for the construction of intracellular pH-sensitive supramolecular block amphiphiles (**Figure 5**). At the physiological pH (~7.4), the hydrophobic BM stalk can bind to the *β*-CD molecule via host-guest interactions. While under acidic conditions (pH < 6), the binding constant of protonated BM/*β*-CD decreases significantly, thus leading to the dissociation of *β*-CD from the BM stalk. In their study, Dox was physically loaded into the supramolecular micelles composed of benzimidazole (BM) modified poly(ε-caprolactone) (BM-PCL) and *β*-CD decorated dextran (Dex-*β*-CD). The Dox release from the micelles was accelerated as expected in an acidic condition, mimicking the endosomal/lysosomal compartments, and the pH-sensitive supramolecular micelles exerted higher inhibition efficiency on the proliferation of HepG2 cells than pH-insensitive analogues.[43]

Figure 5

Voltage stimulus is considered as a clean and simple method in the field of stimuli-responsive polymer systems, in which the system based on *β*-CD and ferrocene (Fc) has attracted considerable attention. The oxidized state of Fc binds

very weakly to CDs because of its cationic nature, while the reduced state of neutral iron binds properly.[17] Yuan et al. prepared voltage-responsive micelles based on the assembly of two biocompatible homopolymers, *i.e.,* β-CD-modified PEG (PEG-β-CD) and Fc-modified poly(L-lactide) (PLLA-Fc). These two homopolymers can form a non-covalent supramolecular amphiphilic block copolymer of PLLA-Fc/PEG-β-CD through the host-guest inclusion between β-CD and Fc, which further self-assembled into core-shell micelles in an aqueous phase. A reversible assembly-disassembly transition of this micellar system was realized by electrochemical control. PTX was loaded into micelles, and the voltage-triggered PTX release was demonstrated. When no stimulus was applied, drug-loaded micelles could exist stably, and the amount of drug released was negligible. However, upon applying a voltage of +1.0 V, the release of PTX was accelerated significantly, accompanied by the disruption of the micelle structure, due to the oxidation of Fc in PLLA-Fc.[44]

2.3 CD-pendant polymers

Polymer with various CD cavities or guest molecules pendant on its side chain can serve as a versatile platform for constructing multi-component supermolecular self-assemblies by non-covalent host/guest inclusion complexation with diverse guest molecules or CDs-modified agents. This strategy offers flexibility, the ease of preparation and high reproducibility in terms of design and development of polymer-based multifunctional delivery systems.

Generally, there are two approaches leading to CD-pendant polymers, direct polymerization of CD-based monomer[45-48] or conjugation of CD derivatives to pre-existing polymers[49-52]. In the first strategy, controlled living radical polymerizations, such as ATRP and RAFT, of CD monomer or together with other monomers can generate CD-pendant polymer with well-defined structure, controlled CD density and various functionalities. However, the preparation of mono-vinyl substituted CD monomers is particularly challenging, due to the presence of multi-hydroxyl groups with equal reactivity located on the CD ring. An alternative towards CD-pendant polymer is to carry out coupling reaction between CD

derivatives and pre-existing polymer with reactive side functions, such as DCC and click couplings, however, this method generally suffers from relatively low grafting density due to the steric hindrance of neighboring reactive side groups by already modified CDs. In the following section, examples will be summarized to provide insights into both methods.

2.3.1 Direct polymerization of CD-based monomer

A common approach to synthesize mono-vinyl substituted CD is to prepare mono-tolylsulfonyl-CD (Ts-CD)[53] first, then convert the tolylsulfonyl group into vinyl group. For example, Ts-CD can be converted into alkyl diamine substituted CD (DA-CD)[54] for subsequent ring-opening reaction with glycidyl methacrylate (GMA) to introduce polymerizable vinyl group to CD.[55] Following this method, Zhang's group synthesized methacrylate substituted *β*-CD (MCD), consisting of both mono- and multi-methacrylate substituted *β*-CD monomers, by ring-opening reaction between ethyl diamino-*β*-cyclodextrin (6-EDA-CD) and GMA. A core cross-linked star polymer was developed by ATRP of this mixture of mono- and multi-methacrylate substituted CDs and 2-(dimethylamino) ethyl methacrylate (DMAEMA) using PEG-Br as a macro-initiator via an arm-first approach. Dox was further loaded into the star polymer for drug delivery. *In vitro* study showed that the DOX-loaded nanoparticles could release their payload in response to the endosomal-pH after being internalized by HeLa cell via a nonspecific endocytosis pathway. At high Dox concentrations, the drug-loaded nanocarriers displayed significantly higher cell cytotoxicity compared to the free drug, indicating the potential of the star polymers for cancer therapy.[56] To obtain pure mono-vinyl substituted CD monomer, an improved method was reported further by the same group. A new mono-methacrylate substituted CD monomer was prepared in a mild reaction condition by simply replacing alkyl diamine with piperazine.[57]

The Ritter's group investigated the synthesis of mono-methacrylate substituted CD monomer *via* click reaction.[58] The effects of two different heating conditions, conventional and microwave heating, on the monomer conformation were studied in

detail. Interestingly, they found that an isomer mixture containing two possible regioisomers was obtained when the reaction was carried out under conventional conditions, whereas reactions performed under microwave irradiation proceeded regioselectively.[58] They further carried out radical copolymerization of microwave-synthesized mono-methacrylate substituted CD with *N*-isopropylacrylamide (NIPAAm) to prepare thermo-responsive polymers with pendant CD. A new anti-cancer polymeric prodrug was developed by host-guest inclusion complexation between the CD-pendant polymer and AD-modified 5-fluorocytosine (5-Fu). The release of the guest anti-tumor agent can be triggered by enzymatic hydrolysis to exert its bioactivity.[59]

2.3.2 Conjugation of CD derivatives to pre-existing polymers

Conjugation of CD to polycation generates promising non-viral gene vectors with excellent transfection efficiency *in vitro* and *in vivo*.[60] The combination of chemotherapy and gene therapy has been repeatedly highlighted by many studies to enhance the therapeutic efficacy in treating cancer due to the synergistic effect.[61-63] For example. Tang and co-workers designed a new supermolecular nanoparticles (SNPs) consisting of host polyethylenimine (PEI)-*β*-CD as the gene vector and guest adamantine-conjugated Dox (AD-Dox) as the chemotherapeutic agent for co-delivery of drug and plasmid. For the synthesis of the host PEI-CD conjugates, the hydroxyl groups of *β*-CD were first treated with 1,1'-carbonyldiimidazole (CDI), and PEI-CD was then prepared by the reaction of CDI-activated CD with the primary and secondary amines of PEI. The guest Ad-Dox was readily produced by coupling reaction between CDI-activated adamantane and the amine group of Dox. The supramolecular PEI-CD/Ad-Dox was obtained via simply mixing, stirring and dialysis in water. PEI-CD/Ad-Dox can further complex with nucleic acid to form pDNA-loaded PEI-CD/Ad-Dox/pDNA SNPs. *In vitro* study in different cell lines indicated that such SNPs could achieve efficient co-delivery of drug and gene to the same cancer cells. Further application of this system for *in vivo* synergistically treating ovarian cancers showed that such delivery system possessed good *in vivo*

retention of chemotherapeutic drugs, achieved efficient therapeutic effects in the inhibition of tumor growth and significantly prolonged the survival time of tumor-bearing mice.[63]

Zhao et al. fabricated polyacrylate-based supermolecular nanoparticles (SNPs) for targeted anti-cancer drug delivery. Dox-loaded SNPs were constructed through the self-assembly of multi-components including *β*-CD-modified polyacrylic acid (PAA-CD), AD-modified polyacrylic acid (PAA-CD), AD-modified PEG (PEG-AD) AD-conjugated fluorescein isothiocyanate (FITC-AD) for fluorescent tracing purposes, AD-modified folate (FA-AD) as a targeting ligand to impart the targeting specificity towards selected cancerous cell lines, and free Dox (**Figure 6**). The resulting SNPs displayed an average diameter of 35 nm, small enough for excellent blood circulation. The cytotoxicity study showed significant cytotoxicity of Dox-loaded SNPs, while the pure SNPs were non-cytotoxic under the same concentrations examined. Due to the presence of FA targeting ligand, the SNPs were highly specific for targeting MDA-MB231 cancer cells, but not for HEK293 healthy cells. The *in vivo* drug delivery of the Dox-loaded SNPs carried out on mouse models with xenogra tumors showed much better efficacy in inhibiting the tumor growth than the SNPs without the folic acid targeting ligand.[64]

Figure 6

Besides AD, a variety of hydrophobic molecules are explored as guests to form inclusion complex with CD. The inclusion of hydrophobic drugs in the cavities of CDs by host-guest interations, as a novel approach for drug loading, enables the formation of CD-pendant polymeric prodrug.

Ma and co-workers synthesized a block copolymer (PEG-*b*-PEDA) with polyaspartamide block containing ethylenediamine (EDA) units. *β*-CD was then covalently linked to this block copolymer to further produce a double hydrophilic block copolymer, PEG-*b*-PCD, consisting of a PEG block and a polyaspartamide block carrying pendant *β*-CD units on the side chain. The cyclodextrin conjugated block can host various guest hydrophobic substances to form inclusion complexes,

while the hydrophilic PEG segment can confer stability to the resultant core-shell nano-assemblies. Diverse hydrophobic drugs such as ibuprofen (IBU), indomethacin (IND), and dexamethasone (DMS) were efficiently loaded into the nanoparticles with significantly improved solubility in their study.[65]

Light, different from the pH gradient in tumor cells, is a controllable external stimulus. Because photo-induced structural change can be realized within seconds or minutes by facilely adjusting the parameters of external light source such as wavelength and intensity,[66] fabrication of photo-responsive polymers provides a popular strategy towards photo-switchable materials for biomedical applications. Azobenzene (Azo) is the most extensively investigated guest for reversible inclusion complexation with CDs. Trans-Azo, stable in visible light, can bind strongly to *α*- or *β*-CD, however, with the irradiation of ultraviolet (UV) light, the Azo molecule will isomerize to the cis state with very weak binding ability to CD.[67,68] Zhang et al. synthesized a light-responsive "plug and play (PnP)" polyanionic template for photo controllable drug delivery based on poly(acrylic acid) (PAA) and *N*-aminododecane glutaric acid *p*-azobenzeneamino containing Azo moiety (**Figure 7**). The *α*-CD-modified molecules, such as α-CD-rhodamine B (*α*-CD-RhB) and *α*-CD-Dox can be loaded onto the pendant CD cavities simultaneously, and could be further released from the template upon UV irradiation driven by the photo-switchable host-guest interaction between *α*-CD and Azo, thus exerting a desirable therapeutic effect on HeLa cells in vitro.[69]

Figure 7

3. Perspective

CDs' commercial availability, facile functionalization, low immunogenicity, biocompatibility and safety have made them excellent candidates for constructing biomaterials. The rapid advance in polymer chemistry has significantly promoted the development of CD-based materials for various biomedical applications during the past two decades. Generally, CD-based polymers can be prepared through either covalent or non-covalent incorporation of CD-containing moieties as building blocks

into the polymer structure. The cavities of CDs incorporated in the polymer can be exploited as the hydrophobic binding sites for diverse bioactive agents (e.g. drug payload and therapeutic target) by non-covalent host/guest inclusion complexation, allowing multivalent conjugations/recognitions, which are often observed in the biological systems. Such intriguing property enables many successful designs and applications of CD-based biomaterials, as demonstrated by extensive investigations on medicine using CD-containing materials including nanoparticles, micelles, vesicles, nanogels, nanopolyplexes, and hydrogels. However, most of these studies remain in the proof-of-concept stage, and only a few therapeutic systems have been thoroughly investigated.

The application of CD-based polymers for drug delivery is a hot subject of research. Although various successful studies have been demonstrated for cancer therapy *in vitro* and *in vivo*, we are still lack of comprehensive evaluations regarding the systemic biocompatibility and toxicology as well as biodegradability of CD-based supermolecular drug delivery systems.

The construction of intelligent CD-based drug delivery systems that are capable of responding to external or internal triggers, such as localized temperature, pH, light, and redox alterations, is an elegant approach towards efficient cancer treatment by providing one solution to the excellent extracellular stability versus effective intracellular drug release dilemma, it is thus anticipated that the fabrication of multi-stimuli responsive inclusion complexes as drug delivery systems will be an active area of research that will create advanced biomaterials for practical applications. Meanwhile, the important extra- and intra-cellular barriers to efficient drug delivery have been comprehensively understood, but most of the reported drug carriers thus far exhibited a lack of functionality for overcoming at least one of these barriers, leading to insufficient efficiency of drug carriers.[19] Therefore it is now desirable to see more sophisticated designs and the generation of drug carriers with integration of multi-functions including stimuli-responsiveness, targetability, detectability, and so on, that can navigate all the obstacles for promising treatment of severe illnesses.

Taken together, the design and development of CD-based drug delivery systems are

in their infancy, and there should be plenty of room for in-depth researches through interdisciplinary collaboration involving polymer chemists, biologists, and scientists of other fields. Looking to the future, we are convinced that CD-based advanced drug delivery systems will eventually be generated to achieve greater control and higher efficacy for cancer therapy.

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Caption of Figures

Figure 1. Molecular structures and dimensions of *α*-, *β*- and *γ*-CDs. Adapted with from Ref. [6]. Copyright (2013) Elsevier.

Figure 2. Schematic illustration of fabrication of supermolecular prodrug micelles based on *α*-CD-hydrazide-Dox·HCl and PEG-*b*-PMPC block copolymer in an aqueous solution, and subsequent controlled release of Dox triggered by endo-/lysosomal pH. Reprinted with permission from Ref. [20]. Copyright (2013) Royal Society of Chemistry.

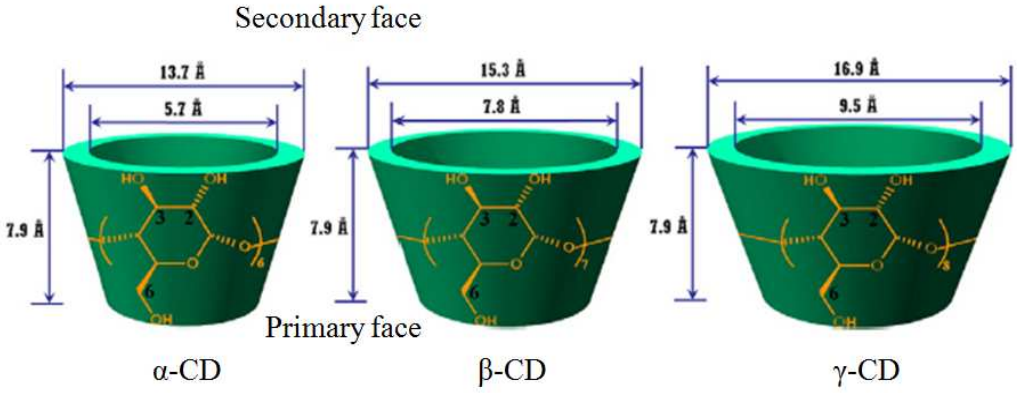
Figure 3. (A) Synthesis of *β*-CD PR and β-CD PR-PTX prodrug, (B) *in vivo* antitumor effect (**p* <0.05 versus Taxols-treated group from the 5th day) and (C) Kaplan–Meier curves showing survival of tumor-bearing mice treated with different formulations at a dosage of 10 mg PTX per kg body weight through intravenous injections. Reprinted with permission from Ref. [23]. Copyright (2013) John Wiley and Sons.

Figure 4. Schematic illustration of *β*-CD polymer-CPT conjugates. Reprinted with permission from Ref. [25]. Copyright (2004) American Chemical Society.

Figure 5. Schematic illustration of Dox loading and intracellular acidic pH-triggered release from Dox-loaded Dex-*β*-CD/BM-PCL micelle. Reprinted with permission from Ref. [43]. Copyright (2013) Royal Society of Chemistry.

Figure 6. Schematic illustration of the formation of Dox-loaded SNPs for tumor-targeted drug delivery. Reprinted with permission from Ref. [64]. Copyright (2014) Royal Society of Chemistry.

Figure 7. Schematic illustration of (A) the light responsive PnP polyanionic template loading and unloading *α*-CD-modified functional groups and (B) target release of loaded *α*-CD-modified functional groups. Reprinted with permission from Ref. [69]. Copyright (2011) John Wiley and Sons.



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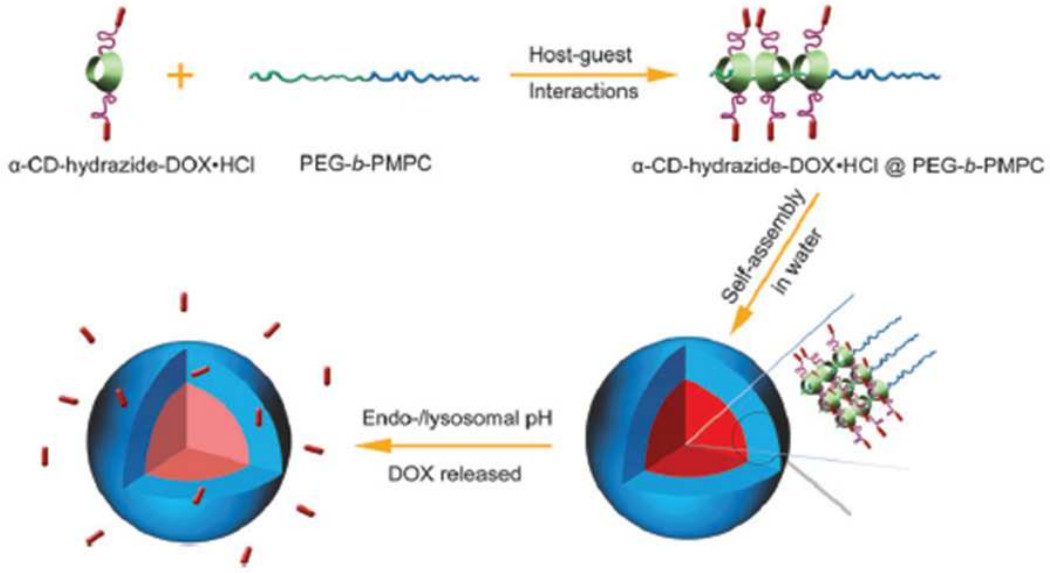

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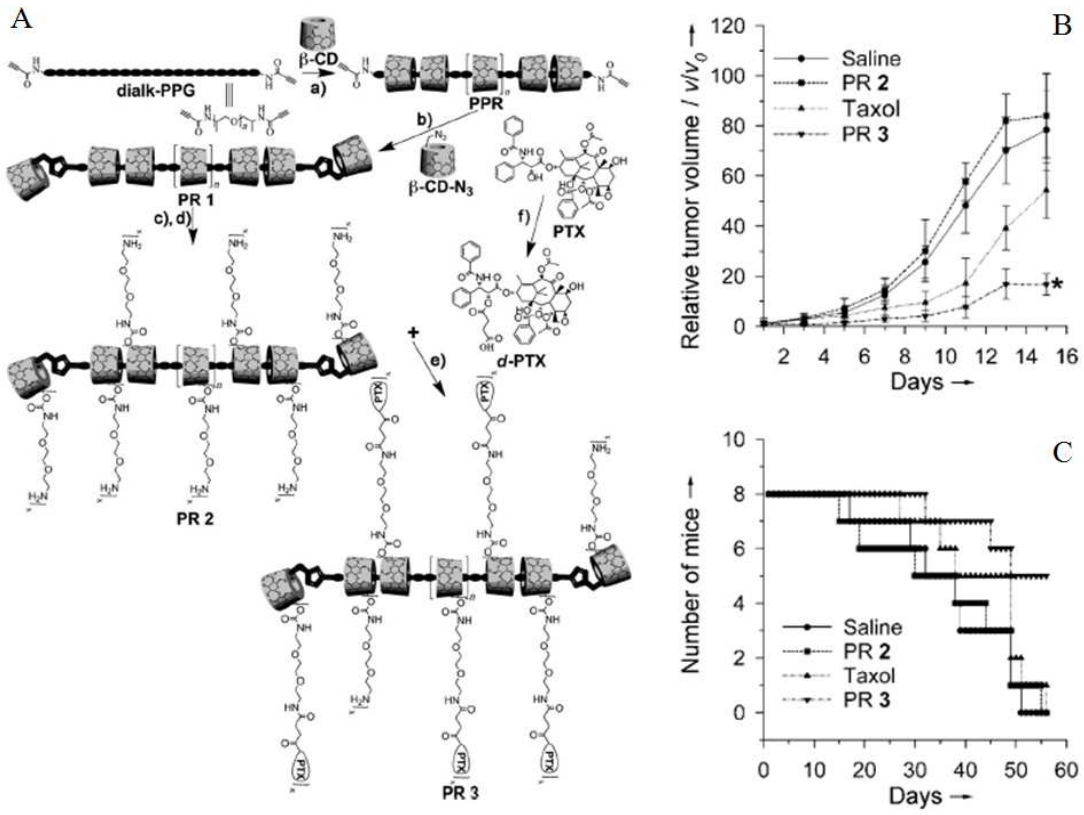

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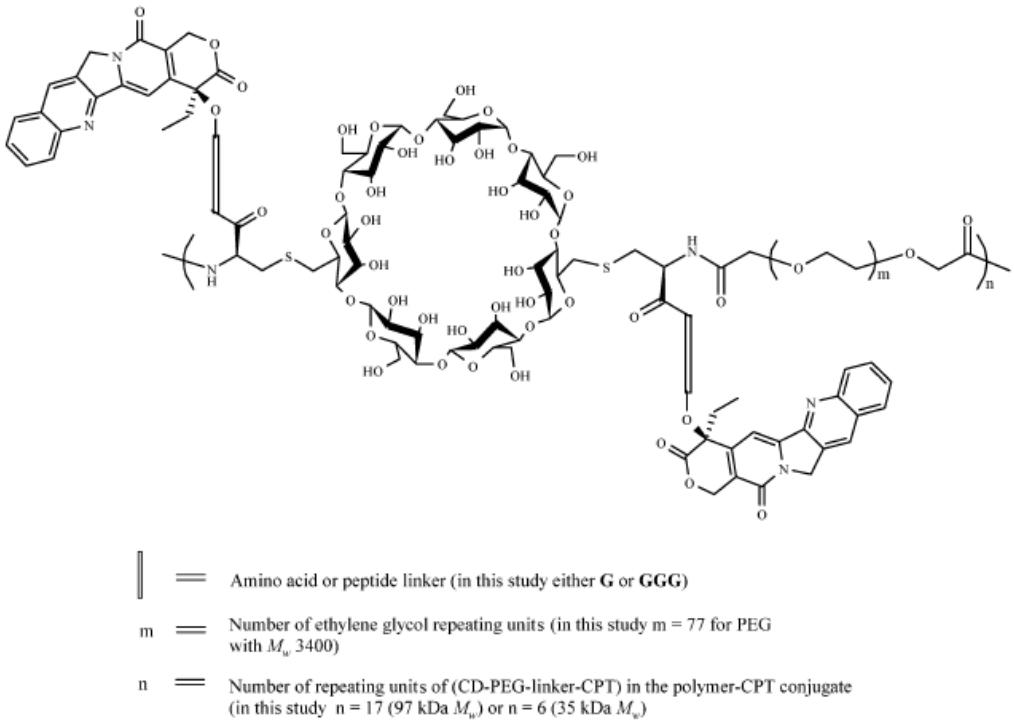

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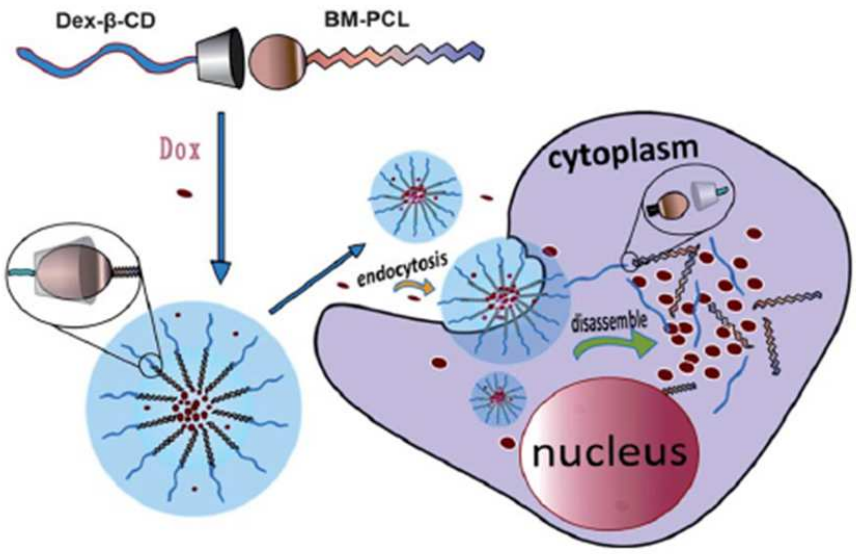

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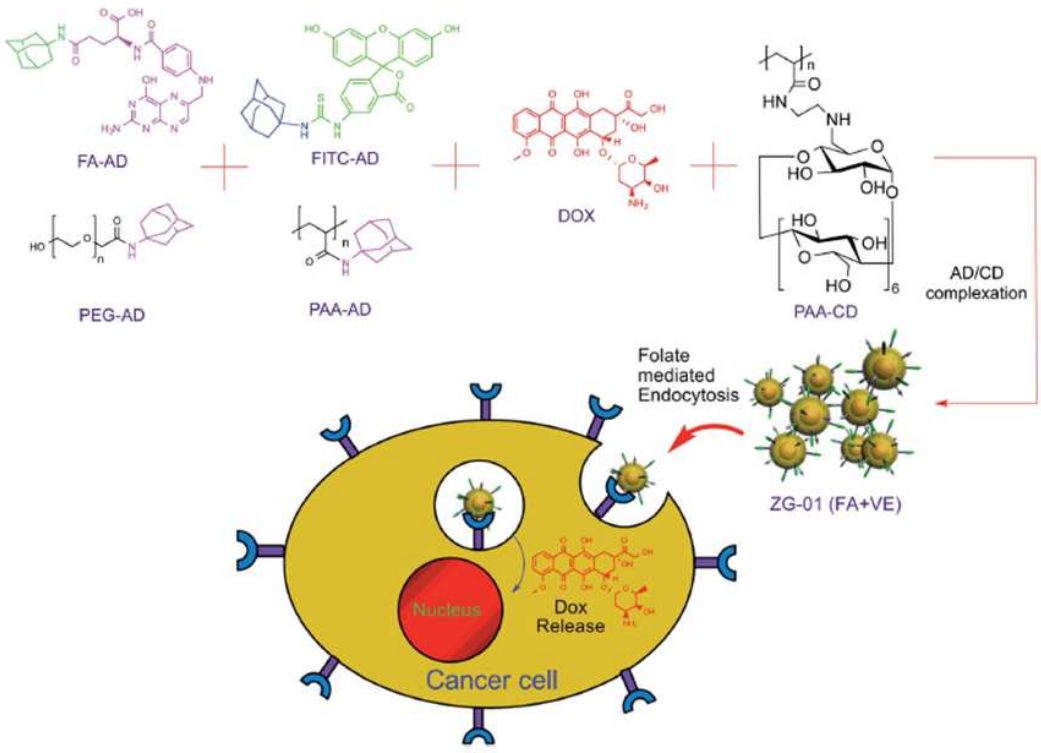

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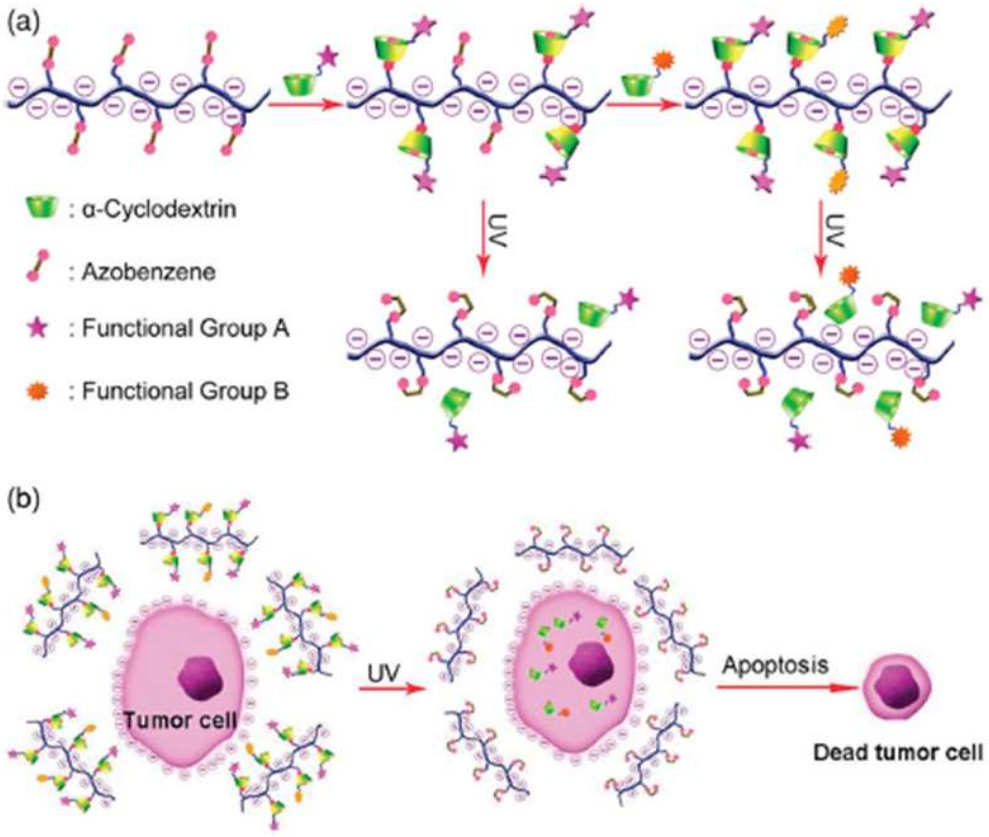

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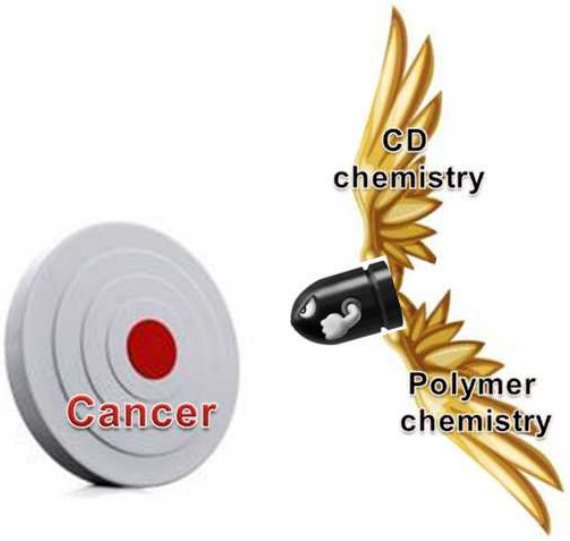
Graphical Table of Content

Cyclodextrin-functionalized Polymers as Drug Carriers for Cancer Therapy

Hua Wei and Cui-yun Yu



This mini-review highlights the recent progress on cyclodextrin-functionalized polymers as drug carriers for cancer therapy.