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REVIEWS

Review

Turn-On Supramolecular Host-Guest Nanosystems as Theranostics for Cancer

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Cancer is one of the world's most serious health challenges. Several problems and challenges still exist for cancer therapies especially because anti-cancer agents that are delivered to normal cells and tissues cause a number of severe side effects. In one general approach aimed at solving this problem, supramolecular systems, created by noncovalent interactions, have been designed and utilized for cancer-cell-targeted drug delivery. In addition, cancer-associated, turn-on supramolecular theranostic agents have received great attention in the biomedicine field because they can be selectively "switched on" in cancer cells. This attribute enables the avoidance of problems associated with cytotoxic effects on healthy cells and tissues. In this review, we summarize recent progress made in the design of turn-on supramolecular theranostic agents composed of host-guest nanosystems and their applications in biomedicine.

INTRODUCTION

Cancer is one of the most life-threatening diseases in the world.[1] However, according to statistics made available in 2017, the annual number of new cases of this disease, including liver and uterine corpus cancers, is still increasing. In light of this, a considerable effort has been devoted over several decades to the development of new technologies for cancer diagnosis and therapy.[2] Perhaps the most critical challenge facing the development of new cancer therapies is associated with the undesirable toxic side effects of anti-cancer agents that are delivered in a nonspecific manner to normal cells and tissues.[3] During this same time period, supramolecular chemistry has emerged as a new field and has provided important techniques for the fabrication of biomaterials such as nano- and micro-particles and hydrogels.[4] As a result of its significance for research, supramolecular chemistry has won two Nobel Prizes. In 1987, Charles J. Pedersen, Donald J. Cram, and Jean-Marie Lehn received the Nobel Prize in Chemistry for their development of crown ethers, carcerands, and cryptands. Additionally, the 2016 Nobel Prize in Chemistry was awarded to Jean-Pierre Sauvage, Sir J. Fraser Stoddart, and Bernard L. Feringa for developing molecular machines. A specific class of substances in this broad family are host-guest complexes that arise from direct hydrophobicity and molecule-size-driven association of host macrocycles (e.g., cyclodextrins, calix[n]arenes, cucurbit[n]urils, pillar[n]arenes, phthalocyanines [Pcs], etc.) with a wide range of guest molecules.[5–8]

Smartly designed macrocyclic host-guest pairs have been applied in new approaches to deal with troublesome issues related to the nonspecificity of cancer therapy. In one of these applications, supramolecular theranostics that are based on host-guest interactions have been designed so that they can be selectively "switched on" in cancer cells, thus avoiding cytotoxicity to healthy cells and tissues. This tutorial review summarizes very recent studies focusing on the design and synthesis of representative turn-on host-guest type nanosystems and their controlled activation by cancer-associated biomarkers (e.g., glutathione, polyamines, specific

The Bigger Picture

Cancer-associated, turn-on supramolecular theranostics have received widespread attention in biomedicine because they can be selectively "switched on" in cancer cells, avoiding cytotoxicity to healthy cells and tissues. This review summarizes recent progress in the development of supramolecular theranostics based on host-guest strategy. Despite the progress made thus far in designing new supramolecular theranostics nanosystems, the development of potent turn-on nanosystems with favorable circulation stability, excellent biocompatibility, and superior anti-tumor efficacy remains a challenge. Understanding the basic principles for improving the performance of building blocks is of great importance for the development of more efficient supramolecular theranostics nanosystems.

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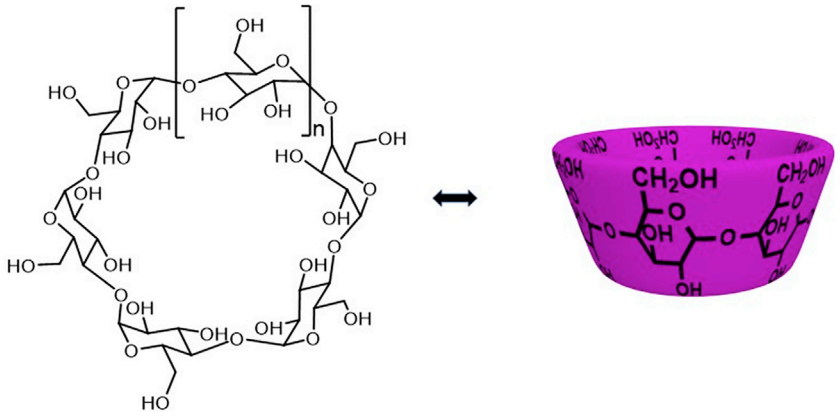

Figure 1. Structures of Cyclodextrins

protein, nucleic acid, reactive oxygen species [ROS], low acidity, and ATP) or exogenous photoirradiation. Host-guest theranostic supramolecular nanosystems can be classified according to their host units, which include cyclodextrins, calixarenes (CAs), cucurbiturils, pillararenes, and Pcs. This classification serves as the basis for the format we have chosen to describe recent observations made in this area.

HOST-GUEST SUPRAMOLECULAR THERANOSTICS NANOSYSTEMS

Cyclodextrins

Cyclodextrins (CDs) are a family of truncated cone-like cyclic oligosaccharides, mostly comprising six to eight D-glucose units linked by α-1,4-glucose bonds, and were discovered by Villiers in 1891. Since that time, CDs have been frequently used in the biomedical field and pharmaceutical industry (Figure 1).[5] CDs have been approved for pharmaceutical preparations in clinical applications (e.g., Bridion). Functionalization of CDs can be achieved by chemical modification of hydroxyl groups on their primary and secondary faces or by the formation of inclusion complexes with guests in their hydrophobic interior cavities.[9] Compared with other frequently encountered macrocyclic receptors, CDs have typically been the first choice for the construction of biocompatible nanosystems for cancer treatment. Consequently, many water-insoluble anti-cancer drugs (e.g., cisplatin, doxorubicin, and paclitaxel [PTX]) have been included into the hydrophobic cavities of CDs through noncovalent interactions in order to promote higher solubility, stability, and bioavailability (Figure 2A).[10,11] Moreover, a number of specific stimuli-responsive triggers can be conveniently incorporated into CDs, thus enabling the controlled and targeted release of theranostic payloads at appropriate times and places. In this respect, numerous stimuli, including physical (e.g., temperature and light), chemical (e.g., pH and redox) and biological (e.g., enzymes), have been employed to trigger the therapeutic performance of CD-based supramolecular nanoassemblies.[12] In addition, disulfide bonds have been employed as intermediate linkers to accomplish drug release in response to natural reducing agents (e.g., glutathione and thioredoxin) in malignant cells.[13] Furthermore, the ferrocene-ferricinium couple has been used to carry out dynamically switchable association-disassociation transitions with β-CD's cavities.[14] Studies have shown that covalent and noncovalent conjugation with a variety of photosensitizers (PSs) (e.g., porphyrin and Pcs)[15] and photochromic molecules[16] can be employed to create photoresponsive CD-based nanoarchitectures. In addition, light-irradiation-related diagnostic and therapeutic functions, such as fluorescence and photoacoustic imaging, as well as photodynamic

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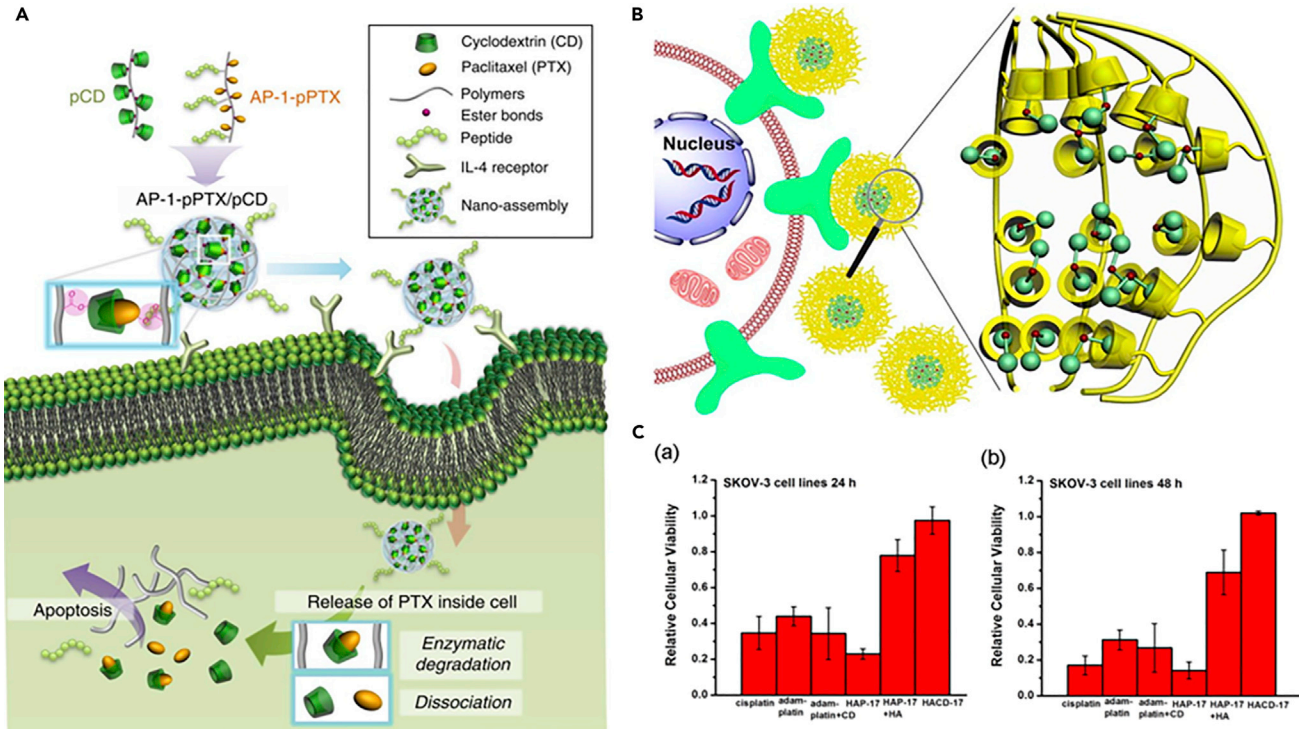

Figure 2. Drug Delivery Using Cyclodextrins

(A) Schematic representation of nano-assembly-mediated PTX delivery. Reproduced with permission from Namgung et al.[11] Copyright 2014 Springer Nature.

(B and C) Schematic representation of targeted polysaccharide nanoparticle for adamplatin prodrug delivery (B) and relative cellular viability of the SKOV-3 cell line (C). Reproduced with permission from Yang et al.[23] Copyright 2013 American Chemical Society.

and photothermal therapies, have been integrated within CD-based supramolecular nanoassemblies, making them promising photoactivable platforms for multimodal anti-cancer therapy.[17] Tian and co-workers[18] assembled the fluorophore-labeled glycoligands and cyclodextrin-capped gold nanoparticle to form a theranostic nanocomposite, which could work as a multimode theranostic system using both the drug-carrying and photodynamic properties of the nanocomposite. In 2017, another successful case using cyclodextrin was the construction of a near-infrared (NIR)-triggered multifunctional nanoplatform that combined fluorescent, photoacoustic, and tomography imaging with gene, chemo-, and photothermal therapy into one nanoparticle.[19] Recently, Lee and co-workers report functional gold nanoparticles (AuNPs) bearing a tumor pH-sensitive γ-cyclodextrin cap, which showed marked potential for tumor therapy.[20]

It is also noteworthy that the synergistic effects caused by combining CD units with polymeric backbones have been used advantageously in the construction of controlled and targeted drug-delivery systems.[21] In these systems, theranostic payloads are effectively bound through multivalent binding of CD units to achieve positive cooperativity, which cannot be easily obtained by employing single or simple host-guest complexation. Moreover, interconnections of biocompatible polymers mediated by CD-containing inclusion complexes usually leads to formation of uniformly sized nanoaggregates as a consequence of a balance between hydrophilic-hydrophobic interactions, which facilitate preferential accumulation in cancerous tissues owing to enhanced permeability and retention (EPR) effects. In this respect, a recent advance in CD-based nanosystems for potential cancer therapy

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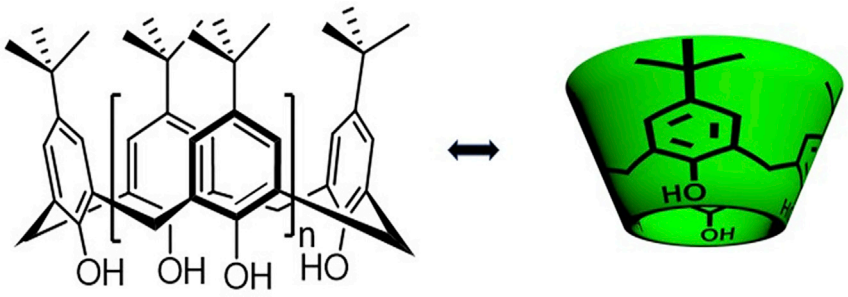

Figure 3. Structures of Calixarenes

has come from the development of CD-grafted hyaluronic acids (HACD), novel types of synthetic polysaccharides that encapsulate different types of hydrophobic cargos and specifically recognize various cancer cells. More recently, the results of theoretical calculations revealed that host-guest interactions, host conformation, and solvation jointly contribute to the drastic stabilization of noncovalent binding between HA derivatives bearing β-CD and adamantane units.[22] In 2013, Liu and co-workers described a conjugated nanoparticle, consisting of adamplatin as the hydrophobic core and HACD as the hydrophilic shell, which exhibits higher anti-tumor activity and lower toxicity both *in vitro* and *in vivo* than conventional cisplatin (Figures 2B and 2C).[23] Since then, HACD-involved therapeutic regimens have been rapidly popularized and a variety of biofunctional counterparts, such as gold nanocluster,[24] inorganic metallic quantum dot,[25] coronene,[26] and small-sized graphene oxide,[27] have been incorporated into the HACD-based supramolecular nanovehicles, which can serve as versatile nanoplatforms for targeted cellular imaging and drug delivery. Another effort demonstrated that a reduction-sensitive multicomponent nanoassembly could be fabricated by inclusion complexation of HACD with adamantane-linked camptothecin (CPT) and naphthalimide, followed by loading a near-infrared absorbing dye into the nanoparticulate assembly.[28]

By viewing the developments that has occurred in this area over the past 5 years, it is clear that, in spite of the advances made in solubilization and transportation of simple CD-drug complexes, the need still exits for drugs that meet the high criteria required for use in the treatment of cancers. As a result, studies aimed at the development of smart theranostic systems, which have high stability and anti-cancer activity and multimodal diagnostic and therapeutic functionalities, have continued. In the following sections, we present a few representative examples of recent progress that has been made in the development of CD-based supramolecular assemblies for anti-tumor drug delivery.

Calixarenes

In a broad sense, CAs are a class of "cyclic oligonuclear phenolic compounds" (Figure 3). In this section, we restrict our discussion to a narrower subclass that includes only CAs that are generated by reactions of formaldehyde with *p*-alkylphenols under basic conditions. Water-soluble CA derivatives, especially the sulfonatocalixarenes (SCAs), which contain sulfonate groups at the upper rim, have shown great potential as multifunctional synthetic receptors that can be utilized for drug solubilization,[29] detoxification of herbicides and nerve agents,[30,31] screening of bioorganic analytes inside live cells,[32] and membrane transport activation of peptide substrates.[33] To further improve the biocompatibility of CA derivatives and explore their compatibility with anionic biomolecules, attention has been given to cationic

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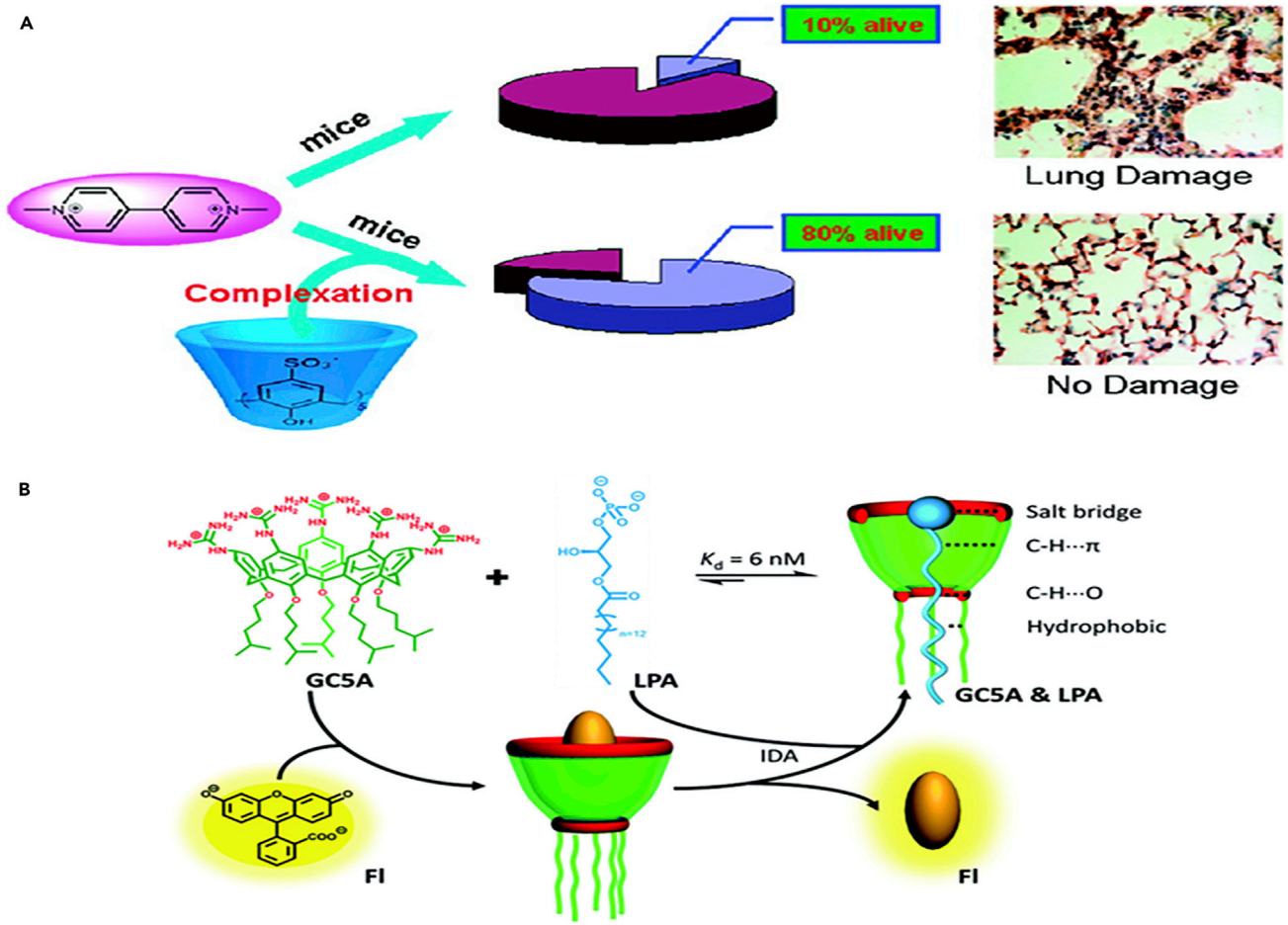

Figure 4. Biological Applications of Calixarenes

(A) Schematic representation of highly effective binding of viologens by *p*-sulfonatocalixarenes for the treatment of viologen poisoning. Reproduced with permission from Wang et al.[30] Copyright 2009 American Chemical Society.

(B) Schematic illustration of the binding between lysophosphatidic acid (LPA) and guanidinium-modified calix[5]arene (GC5A) and the operating indicator displacement assay principle of fluorescence "switch-on" sensing of LPA by the GC5A-fluorescence reporter pair. Reproduced from Zheng et al.,[39] published by the Royal Society of Chemistry.

CAs. In this regard, guanidinocalixarenes (GCAs) have emerged as important substances because of their high-water solubility, convenient methods for synthesis and high biosafety. Because of limited space, our discussion focuses only on recent achievements that have been made in studies of GCA-based supramolecular nanosystems. Readers who desire a more thorough discussion of the CA family and related biological applications of SCAs should consult a recently published monograph[34] and several reviews.[6]

Besides increasing water solubility, introduction of sulfonate and guanidinium groups into the calixarene scaffold has two other effects (Figure 4). First, the presence of multiple ionic substituents in conjunction with the preorganized macrocyclic structures of CAs greatly promotes self-aggregation and enhances the stability of self-assemblies of amphiphilic and π-aromatic molecules by decreasing their critical aggregation concentration and regulating aggregation modes.[35] Second, water-soluble CAs bearing polar head groups that serve as anchoring points can form highly stable inclusion complexes with oppositely charged organic dyes and PSs.

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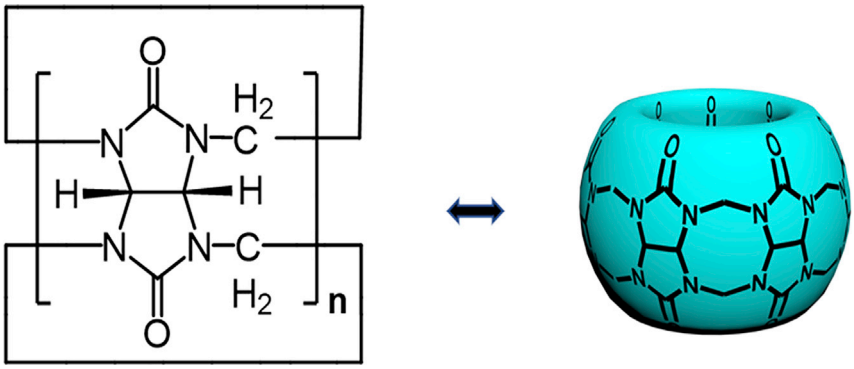

Figure 5. Structures of Cucurbit[n]urils

In this way, the excited states of guest molecules can be quenched enabling manipulation of photophysical properties that are applicable to tandem assays and phototheranostics.[36]

In previous studies, a series of multi-substituted GCAs containing have been developed as gene delivery vectors for enhanced DNA condensation and transfection with reduced cytotoxicities in various cell lines.[37] In spite of these findings and compared to their extensively investigated CD-based counterparts, CA-based nanosystems represent a new arena for the discovery of protocols for cancer diagnosis and treatment.[38] In one study focusing on this issue, the new guanidinium-modified GCA receptor, GC5A (Figure 4B), with multiple hydrophobic tails located at the lower rim was ingeniously designed.[39] This novel GCA was found to display nanomolar binding to lysophosphatidic acid (LPA), an important biomarker for ovarian cancer, particularly its early stage. The extraordinarily strong binding affinity was attributed to the orderly threading of alkyl chains of LPA into the hydrophobic region of GCA and charge-assisted hydrogen bonding between the phosphate of LPA and guanidinium head groups in GC5A. Equally important, by using a GC5A along with a fluorescent indicator displacement assay and differential sensing method, lysophosphatidic acid can be accurately determined in untreated serum with a detection limit at the micromole level.

Although at an early stage, this study has provided results that hint at a potential practical method for diagnosis of early-stage gynecologic tumors. It is clear that the field of CA-based supramolecular theranostics is in its infancy. However, because derivatives containing upper- and lower-rim modifications can be prepared in a facile manner, it is expected that many new CAs with fascinating physio-chemical properties will be explored as nanoplatforms for cancer therapy. Moreover, through innovative multidisciplinary collaborations, versatile strategies for biomedical applications of CA-based bioactive nanosystems should become available in the near future.

Cucurbit[n]urils

Cucurbit[n]urils (CB[n]), including CB[5], CB[6], CB[7], CB[8], and CB[10], are macrocyclic containers that are synthesized by acid-catalyzed condensation of glycoluril units with maldehyde (Figure 5).[7,40] In 1905, Behrend and co-workers prepared the first CB[n], but its constitution remained unclear until 1981 when Mock and co-workers assigned its remarkable macrocyclic structure and dubbed the compound cucurbituril because of its resemblance to a pumpkin.[41] As a result of the presence

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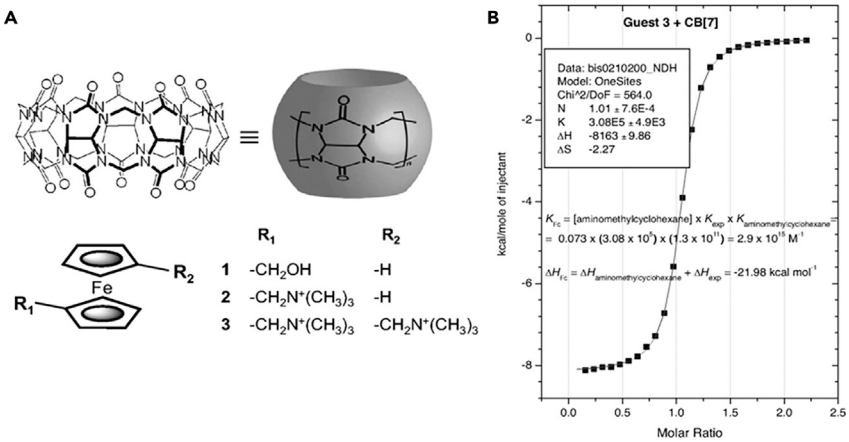

Figure 6. Forming Stable Inclusion Complexes by Using Cucurbit[n]urils

Structures of the host cucurbit[7]uril (CB[7]) and ferrocene guests (A) and competition isothermal titration calorimetry experiments on complexation of 3 with CB[7] (B). Reproduced with permission from Rekharsky et al.[50] Copyright 2007 National Academy of Sciences.

of a hydrophobic cavity and a pumpkin-like shape containing two hydrophilic carbonylated rims, CB[n]s form stable 1:1 and 2:1 host-guest complexes with a variety of inorganic and organic guests. In comparison with CDs and CAs and because their isolation and identification did not take place until around 2000, CB[n]s have a relatively short history of being components of host-guest supramolecular nanosystems.[42] However, CB[n] have now begun to play an important role in supramolecular chemistry and, accordingly, the number studies in this area has increased dramatically in the past decades.[43,44]

CB[n]s have shown great potential in the biomedical field because of their strong binding interactions and low toxicity.[45] As a prelude to applications of CB[n]s, Nau and co-workers conducted a comprehensive assessment of their toxicities.[46] The results of *in vitro* cell studies indicate that CB[n]s have sufficiently low toxicities.

Interestingly, the cavity sizes of the CB[n] members, CB[6], CB[7], and CB[8], are similar to those of the corresponding α-, β-, and γ-CDs. Although poor water solubility limits their applications in the biomedical field, the solubilities of CB[n]s can be enhanced by acids and alkali metal ions or by introducing functional groups.[47]

CB[n]s have extremely high affinities toward some guest molecules typically used in supramolecular chemistry. In 2005, Kim and co-workers showed that ferrocene and its derivatives form highly stable inclusion complexes with CB[7], with high binding constants in the respective 10^9–10^{10} M^{-1} and 10^{12}–10^{13} M^{-1} ranges.[48,49] An even higher equilibrium association of around 10^{15} M^{-1} was observed in 2007 (Figure 6).[50] Therefore, CB-based supramolecular assemblies have received wide attention as anti-tumor drug-delivery systems.

Pillar[n]arenes

Pillar[n]arenes (P[n]As)[8,51,52] are a class of pillar-shaped macrocyclic hosts that have a shorter history in the area of supramolecular chemistry compared to other types of macrocyclic molecules, including CDs, CAs, and CBs (Figure 7). In 2008, Ogosh and co-workers described the first P[n]As, which have symmetrical pillar architectures composed of hydroquinone units linked by methylene bridges at their

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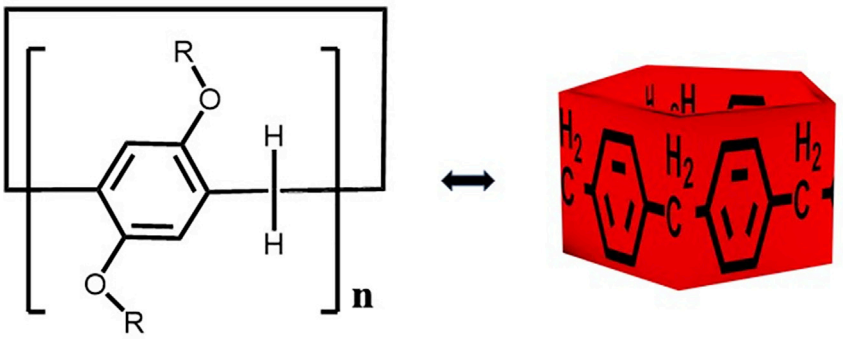

Figure 7. Structures of Pillar[n]arenes

para-positions (Figures 8A and 8B).[53] P[n]As and their derivatives have recently attracted great interest owing to their unique architectures, and facile high-yielding synthesis and derivatization.[52] In recent years, P[n]As, which possess unique rigid pillar architectures, have been increasingly utilized to construct smart nanomaterials such as vesicles,[54] artificial transmembrane channels,[55] molecular machines,[56] liquid crystals,[57] porous materials,[58] and supramolecular polymers.[59]

P[n]As have several advantageous features that make then versatile building blocks for the construction of stimuli-responsive supramolecular assemblies.[60] For example, these macrocyclic substances have symmetrical pillar-shaped structures and planar stereogenicities. Moreover, owing to the presence of electron rich arene-lined cavities in P[n]As, stable host-guest complexes can be formed with neutral molecules via multiple CH/π interactions. Lastly, versatile methods have been developed for the preparation and functionalization P[n]As, and as a result, various types of trigger groups can be easily incorporated into in these substances to create smart supramolecular assemblies.

P[n]As containing simple alkyl and phenolic substituents are not water soluble and are thus difficult to use in new medicinal platforms. However, the water solubilities of P[n]As can be easily enhanced by introducing hydrophilic groups in both rims. For example, Ogoshi et al.[61] designed a water-soluble pillar[5]arene, which contains ten water-solubilizing, hydrophilic carboxylate anion groups surrounding the core. In addition, Huang and co-workers[62] developed the water-soluble pillar[6]arene, **WP6**, which contains 12 carboxylate moieties and whose water solubility can be reversibly regulated by changing the pH of the solution (Figure 8C). Moreover, **WP6** forms stable host-guest complexes (**WP6⊃G1**) with pyrene tethered pyridinium salts **G1**, which self-assemble into vesicles. Reversible dispersion of **WP6⊃G1** in multiwalled carbon nanotube form in water can be pH controlled. Another successful case using carboxylatopillar[6]arene is the constructing of pH responsive drug-delivery system for anti-cancer agent oxaliplatin, which would be protected by forming host and guest compounds and then released selectively in the acidic tumor.[63] Other useful methods of producing water-soluble P[n]As are through modification of their rims with cationic moieties[64] and nonionic oligo(ethylene oxide) chains.[65] Water-soluble P[n]As have begun to play an important role in supramolecular theranostics nanosystems.

Phthalocyanines

Pcs[66] are macrocyclic aromatic compounds that were accidentally discovered in Scotland in 1928 during the industrial production of phthalimide. Pcs, as synthetic

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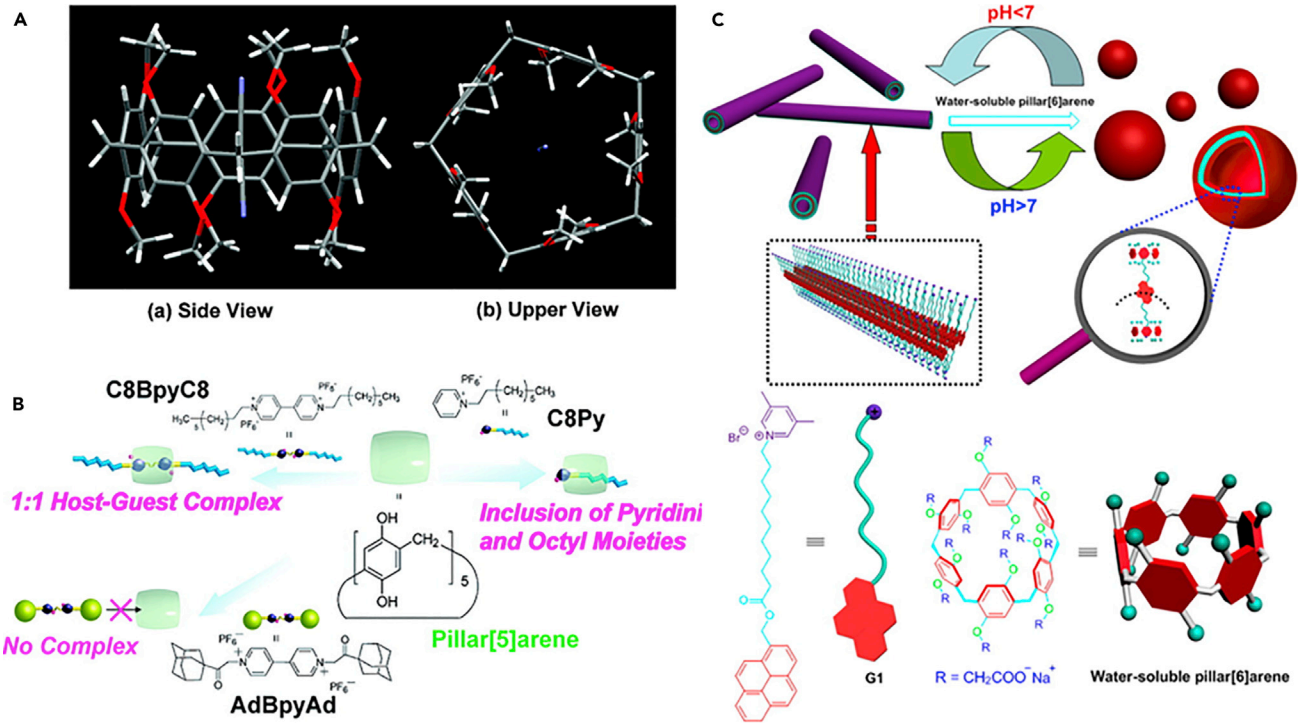

Figure 8. Constructing Smart Nanomaterials by Using Pillar[n]arenes

(A and B) Crystal structure of DMpillar[5]arene (A) and host-guest complexes of pillar[5]arene with guest molecules (B). Reproduced with permission from Ogoshi et al.[53] Copyright 2008 American Chemical Society.

(C) Schematic representations of the reversible transformations between G1 nanotubes and WP6⊃G1 vesicles (top) and the structures of WP6 and G1 (bottom). Reproduced with permission from Yu et al.[62] Copyright 2012 American Chemical Society.

porphyrin analogs, have demonstrated great potential for use in smart materials that have practical applications in various disciplines (Figure 9).[67,68] Over the last few decades, Pcs have shown great advantages for use as efficient photosensitizers in photodynamic therapy (PDT) because of their long absorption wavelengths (λ_{max} > 670 nm), high extinction coefficients, and high photostabilities.[69] Moreover, long triplet-excited-state lifetimes and high quantum yields for their formation, both needed for their use as efficient PSs, can be achieved by coordination of diamagnetic metals such as silicon, zinc, or aluminum in the Pc cavities. As a result of their high degrees of stacking and the nature of the central metal ion, Pcs form highly ordered functional assemblies in solution and on surfaces.[70]

EXAMPLES OF CANCER-ASSOCIATED STIMULI-DRIVEN TURN-ON SUPRAMOLECULAR THERANOSTIC NANOSYSTEMS BASED ON HOST-GUEST INTERACTIONS

Glutathione-Driven Turn-On Supramolecular Theranostic Nanosystems

Smart theranostic nanosystems, especially those that respond to biomarkers present in diseased cells, hold great importance in future clinical applications. As a cellular protection agent, glutathione (GSH, γ-glutamyl-cysteinyl-glycine) controls a number of cellular processes such as metabolism, balancing carcinogenicity, antioxidant defense, and cell differentiation.[71] In addition, GSH serves as an antioxidant to protect cells by trapping free radicals and plays a key role in the control of oxidative stress in redox homeostasis. Moreover, abnormal levels of GSH are potential biomarkers for many diseases, including cancer, liver and lung damage, and Parkinson's disease.[72]

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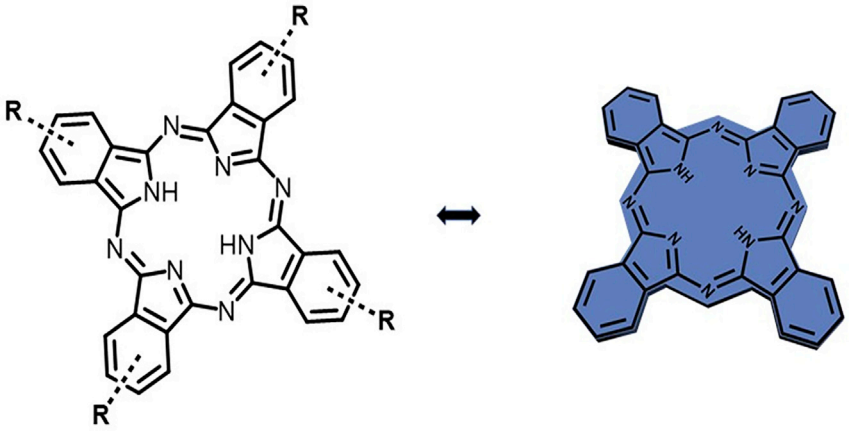

Figure 9. Structures of Phthalocyanines

Given the fact that its concentration in tumor cells is 100- to 1,000-fold higher than that in the extracellular microenvironment, GSH is an excellent promoter of selective intracellular drug release in tumor cells microenvironment.[73]

Recently, Chen and co-workers[74] described a GSH-driven turn-on supramolecular theranostic nanosystem composed of a β-cyclodextrin-based polyrotaxane. The key design feature of this theranostic system, which displays dual-responsive drug release, and the details of its function are illustrated in Figure 10A. The supramolecular nanosystem is composed of an assembly of an amphiphilic diblock copolymer (axle) and the primary-amine containing β-cyclodextrin (wheel) created by host-guest complexation. The core-shell structured nanoparticles, formed as a consequence of π-π stacking interactions between perylene dyes and hydrophobic interactions of poly(ε-caprolactone), can be employed to load hydrophobic anti-cancer drugs. In general, nanoparticles formed from block copolymers enhance the efficacy of drugs because of their ability to promote cellular uptake through enhanced permeability and retention (EPR) effect. However, premature release of loaded drugs is a concern when using nanoparticle carrier systems. However, formation of shell-crosslinked nanoparticles (SCNPs) effectively inhibits premature drug leakage. Moreover, introduction of disulfide bonds enables SCNPs to respond to intracellular GSH, which induces specific drug release inside cells. The smart topological structure of polyrotaxane significantly enhances the maximum tolerated dose (MTD) of this theranostic nanosystem. The cyclic peptide cRGDfK serves as the stopper in the complex to endow this supramolecular nanosystem with a cancer-cell-targeting ability. The results of this study show that the anti-cancer drug CPT can be encapsulated in the supramolecular platform with a loading content of 43.2%. *In vitro* and *in vivo* studies demonstrate SCNPs@CPT displays an excellent anti-tumor performance and anti-metastatic effect. Importantly, observations made in this effort will aid the design of next-generation nanocarriers for cancer treatment.

Pei and co-workers[75] designed the novel ferrocenium capped amphiphilic pillar[5]arene (**FCAP**) and showed that it serves as a GSH-responsive system for drug and siRNA co-delivery in aqueous solution (Figure 10B). The anti-cancer agent doxorubicin hydrochloride (DOX) was selected as a model drug for assessing the release properties of this nanocarrier. DOX encapsulation in the nanocarrier was found to be 67.0% by a UV-visible (UV-vis) absorption spectroscopy-based assay. This result shows that the cationic vesicles formed by **FCAP** possess a high drug-loading capacity. Moreover,

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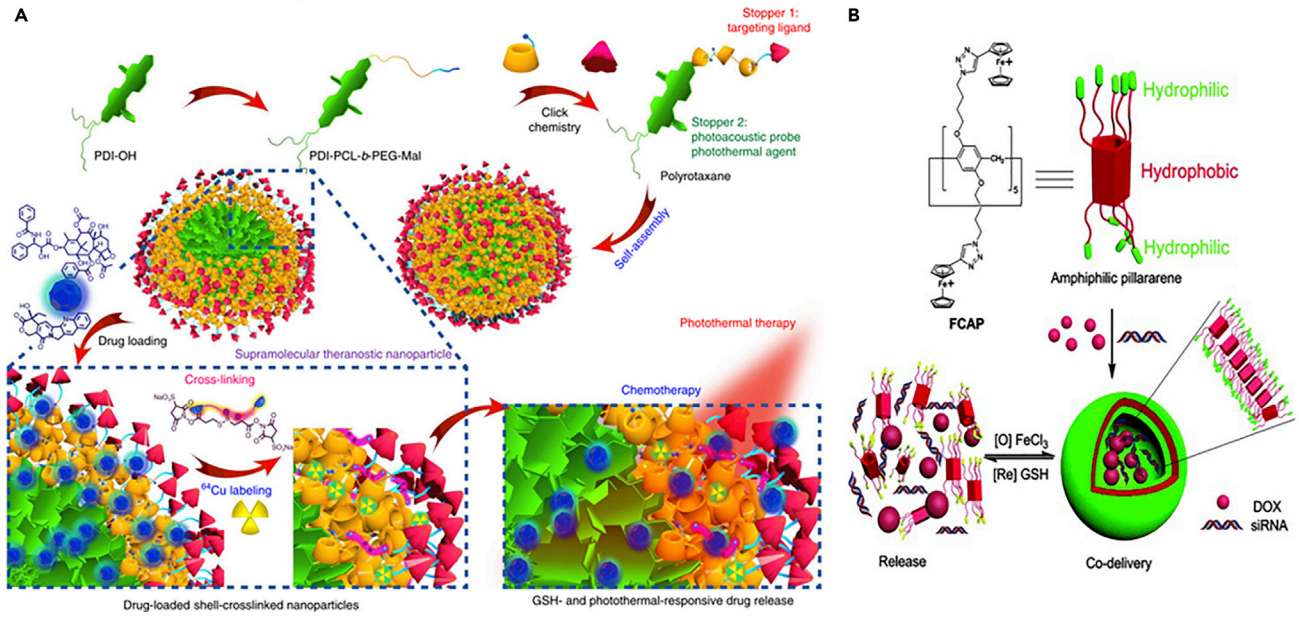

Figure 10. Glutathione-Driven Turn-On Supramolecular Theranostic Nanosystems

(A) Schematics of the synthesis and fabrication of scnps for supramolecular theranostics. Reprinted from Yu et al.[74] under the CC BY 4.0 license.

(B) Illustration of the formation of cationic vesicles and their redox-responsive drug and siRNA release. Reprinted with permission from Chang et al.[75] Copyright 2014 Wiley-VCH Verlag GmbH & Co. KGaA.

the cationic vesicles display low cytotoxicity in normal cells and rapid drug release and gene transfection in cancer cells that contain relatively high GSH concentrations. Moreover, this is the first example of a redox-responsive drug and siRNA co-delivery nanocarrier based on amphiphilic pillar[5]arene and of a GSH-responsive system that shows potential applications in overcoming drug resistance of cancer cells.

Polyamine-Driven Turn-On Supramolecular Theranostic Nanosystems

In spite of the new therapeutic developments that have occurred recently, chemotherapy is still an indispensable clinical anti-cancer strategy. However, because chemotherapeutic agents do not distinguish between cancer and normal cells, numerous challenges such as severe side effects and poor anti-tumor efficacy confront the clinical use of chemotherapy in clinical practice. Interestingly, by employing a strategy in which supramolecular chemistry is combined with chemotherapy, anti-tumor agents can be disguised within macrocyclic hosts and released in a tumor-cell-specific manner (Figure 11). As a result, they exhibit low cytotoxicity in normal cell environments.

Polyamines, which are alkylamines that contain multiple amine groups, exist in nearly all prokaryotic and eukaryotic cells, where they play key roles in cellular activities.[76] Importantly, polyamines are indispensable organic polycations in living organisms and are thought to serve multiple functions and applications in biological processes.[77] However, because polyamines such as spermidine and spermine are both overexpressed in many types of cancer cells and play essential roles in the regulation of tumor cell growth, they are potential biomarkers for many types of cancers, such as colorectal cancer and lung cancer.[78]

By using this strategy, Zhang and co-workers[79,80] designed a polyamine-driven turn-on, supramolecular system for modulating cytotoxicity in chemotherapy

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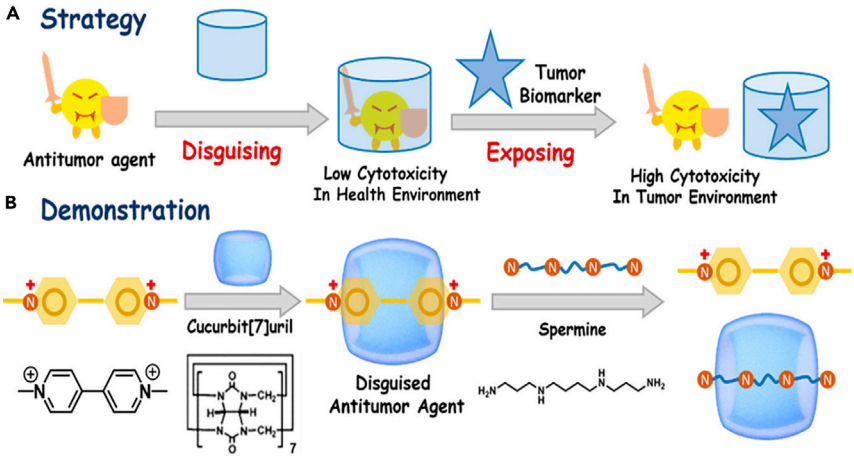

Figure 11. Schematic Representation of Supramolecular Chemotherapy
(A) Controlling disguise and exposure of anti-tumor agents by host-guest chemistry.
(B) Demonstration of this concept using dimethyl viologen, cucurbit[7]uril, and spermine.
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(Figure 11). In this approach, the release of the anti-tumor agents dimethyl viologen (MV) and oxaliplatin (OxPt) and consumption of spermine in the tumor cell are controlled by cucurbit[7]uril (CB[7])-mediated host-guest interactions. The disguised anti-tumor agents recover their anti-tumor activity in tumor cells as a result of their competitive displacement by spermine. Host-guest complexation enables this new supramolecular to exhibit higher anti-tumor activities than do the guest agents themselves. Two factors are responsible for this phenomenon. First, the anti-tumor activity of the guest drug is recovered by competitive replacement of spermine from the macrocyclic host CB[7]. Second, by host-guest interactions the host CB[7] consumes spermine in tumor environments, further reducing the viability of cancer cells.

Very recently, Zhang's group developed a method for supramolecular chemotherapy that utilizes carboxylated pillar[6]arene (CP[6]A) as the host molecule to decrease the cytotoxicity of OxPt in normal cells and improve its anti- colorectal cancer efficacy.[81] In this system, the guest OxPt is released from the cavity of the macrocyclic host by competitive displacement with spermine, which has a higher binding affinity for the host. However, when CB[7] is utilized as the host the amount of free OxPt is limited in a concentration-dependent manner by this reversible competitive replacement of process. To deal with this problem, CP[6]A was used in the supramolecular chemotherapy system because it has a higher binding affinity for spermine over that of OxPt in the tumor cells. Specifically, the binding affinity between CP[6]A and OxPt at physiological pH (7.4) was found by isothermal titration calorimetry (ITC) to be $1.66 \times 10^4\ M^{-1}$, which contrasts with the binding constant of $2.58 \times 10^7\ M^{-1}$ between CP[6]A and spermine. A Job plot for complex formation between CP[6]A and OxPt obtained by UV-vis spectroscopy showed that CP[6]A encapsulates OxPt with a 1:1 binding stoichiometry. Importantly, the results of *in vitro* cell experiments clearly demonstrate that CP[6]A reduces the normal cell cytotoxicity of OxPt through host-guest complex formation.

Specific-Protein-Driven Turn-On Supramolecular Theranostic Nanosystems

Proteins are biomacromolecules that consist of chains of amide linked amino acid residues. Many proteins are enzymes that catalyze biochemical reactions essential for metabolism in living organisms. Moreover, abnormal expression of specific

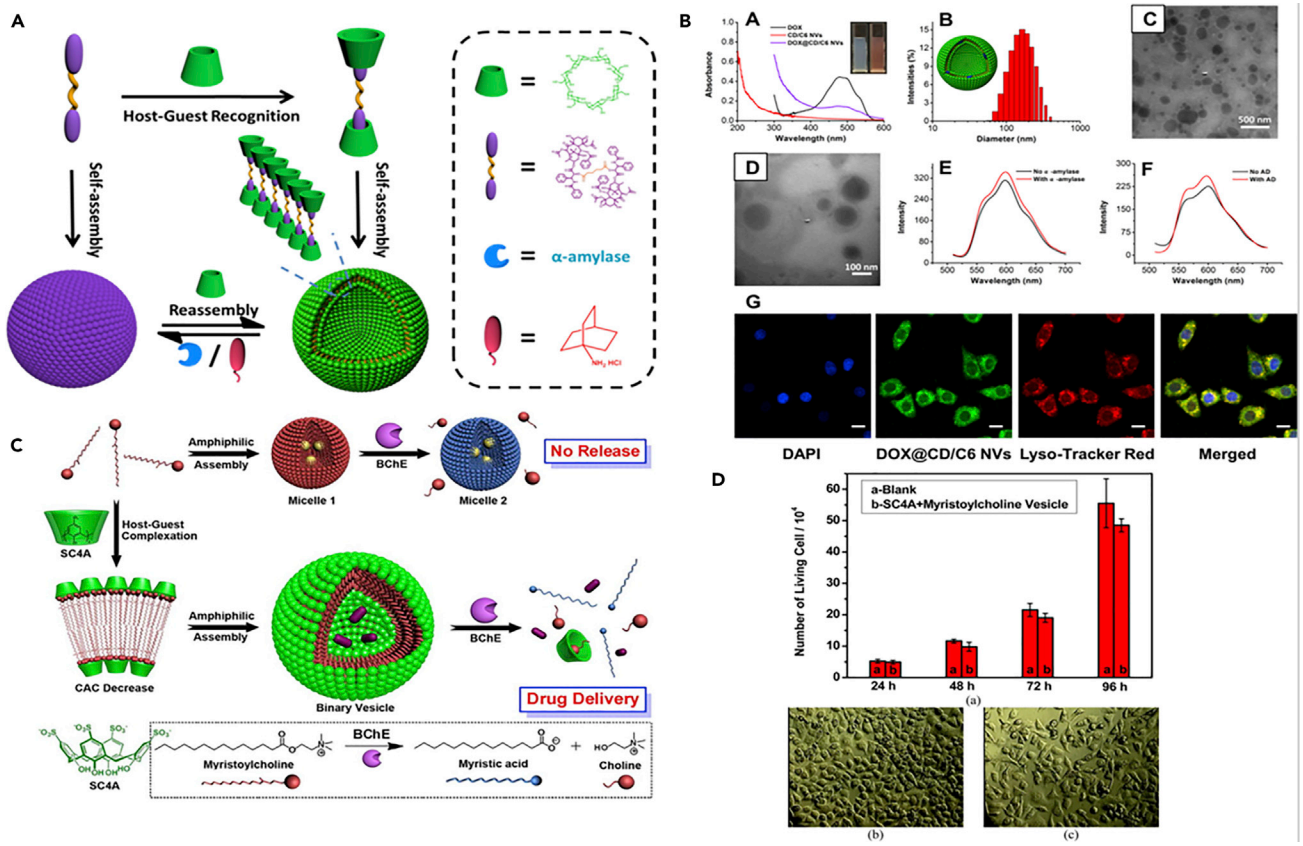

Figure 12. Specific-Protein-Driven Turn-On Supramolecular Theranostic Nanosystems

(A) Schematic illustration of the complexation between PTX dimer and CD and their reversible structural transformation between nanoparticles and vesicles induced by dual stimuli (α-amylase and adamantanamine hydrochloride [AD]).

(B) (a) UV-vis spectra of DOX, CD/C6 NVs, and DOX@CD/C6 NVs. (b) Size distribution and schematic view (inset) of DOX@CD/C6 NVs. (c) TEM image and (d) enlarged TEM image of DOX@CD/C6 NVs. (e and f) Fluorescence intensity changes of DOX@CD/C6 NVs induced by α-amylase and AD. (g) Confocal laser scanning microscopy (CLSM) images of HepG2 cells incubated with DOX@CD/C6 NVs at 37°C for 1.5 h. From left to right: cell images dyed with 4′,6-diamidino-2-phenylindole (blue), DOX@CD/C6 NVs (green), and LysoTracker Green (red) and their merged images.

(C) Schematic illustration of amphiphilic assemblies of myristoylcholine in the absence and presence of SC4A.

(D) Number of living LO2 cells in the blank group and after treatment with SC4A plus myristoylcholine vesicle from day 1 to day 4 (a) and images of living LO2 cells in the blank (b) and SC4A plus myristoylcholine vesicle (c) groups after 72 h.

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(C and D) Reproduced with permission from Guo et al.[84] Copyright 2012 American Chemical Society.

enzymes is usually related to diseases.[82] A large number of enzyme biomarkers are associated with cancer and thus can be used for cancer diagnosis and treatment. Therefore, specific-protein-driven turn-on supramolecular host-guest-based theranostic nanosystems have been developed and demonstrated to be highly efficient and specific theranostic agents.

Xie and co-workers[83] showed that enzyme responsive supramolecular binary vesicles are formed by host-guest interaction of β-cyclodextrins (β-CDs) and the dimer of the anti-cancer drug PTX (Figure 12A). The strong hydrophobicity of PTX limits its applications as an anti-cancer drug for treatment of a wide range of solid tumors. The development of nanoscale PTX is an effective approach to improve its solubility and increase its accumulation in tumor sites. Studies of host-guest complexation between β-CDs and PTX dimer in water by using proton nuclear magnetic resonance spectroscopy show that an inclusion complex forms and that the

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complex self-assembles into higher-order vesicles. The loading content and loading efficiency of the anti-cancer drug DOX in the vesicles are 6 wt % and 81%, respectively. It was demonstrated that DOX is encapsulated into the vesicles by observing a band from 420 to 550 nm in the UV-vis absorption spectrum in association with a light pink (Figure 12Ba). TEM images showed that the vesicles have a spherical shape (Figure 12Bb–12Bd). In addition, dual external stimuli α-amylase and adamantanamine hydrochloride (AD) serve as dual stimuli to promote the release of the loaded anti-cancer drugs by causing degradation of the hydrophilic CD layer.

An interesting cholinesterase-responsive supramolecular vesicle system was developed with the macrocyclic host p-sulfonatocalix[4]arene and cholinesterase-cleavable myristoylcholine as a guest (Figure 12C).[84] p-Sulfonatocalix[4]arene forms a stable inclusion complex with myristoylcholine, which acts as a superamphiphile to create enzyme-responsive supramolecular vesicles. The vesicles are dissipated with high specificity and efficiency by using cholinesterase. The results of basic cell experiments showed that these supramolecular vesicles are practically nontoxic and therefore that they can be used as an ideal nanocarrier for drug delivery.

Nucleic-Acid-Driven Turn-On Supramolecular Theranostic Nanosystems

Specific nucleic acid sequences are closely associated with certain stages of various diseases, and as a result, they can be utilized as reliable biomarkers for cancer diagnosis.[85] In addition, because of its spatiotemporal selectivity and noninvasive characteristics, PDT is a promising approach for cancer treatment. However, recent studies have demonstrated that PDT systems composed of traditional PSs have "Achilles' heels."[86] Specifically, patients are required to remain in the dark for relatively long periods of time after PDT treatment. This restriction results from the fact that "always on" PSs generate harmful photosensitization effects on normal tissues upon exposure to indoor light and sunlight. In addition, the hypoxic microenvironment of tumor tissues causes severe resistance to PDT which requires molecular oxygen to generate ROS.

Recently, Yoon, Huang, and co-workers[87] designed a nucleic-acid-driven turn-on supramolecular theranostic nanosystem, **PcS-MA**, that overcomes the drawbacks of PDT (Figure 13). This system was created with phthalocyanine (**PcS**) as a water-soluble fluorescent host and the anti-cancer drug mitoxantrone (**MA**) as a stable guest. The excited state of **PSc** in this nanosystem is 96.7% quenched, and thus it is incapable of promoting ROS ($^1O_2$) generation. However, disassembly of the supramolecular nanosystem promoted by an external stimulus in cancer cells releases free **MA** (which strongly binds to DNA) and unquenched **PSc** (which fluoresces and has the ability to generate $^1O_2$). Moreover, as a result of an EPR effect and selective turn on in tumor cells, the supramolecular theranostic nanosystem **PcS-MA** displays a good therapeutic effect.

ROS-Driven Turn-On Supramolecular Theranostic Nanosystems

ROSs include superoxide ($[O_2]^{\cdot-}$), hydroxyl radical ($[OH]^{\cdot}$), hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), $^1O_2$, and peroxynitrite ($ONOO^-$). Because of mitochondrial malfunction caused partially by oncogenic stimulation and increased metabolic activity, cancer cells contain higher levels of ROS than do normal cells.[88]

Recently, Zhao and co-workers developed a polymer-based, dual ROS- and pH-responsive nanoparticle for *in vivo* drug delivery.[89] This system, constructed by a supramolecular approach, is loaded with the anti-cancer drug DOX (Figure 14A). Incorporation of disulfide bonds in the polymer network endowed the dual responsive nanoparticles with the ability to release DOX in the endoplasm of cancer cells.

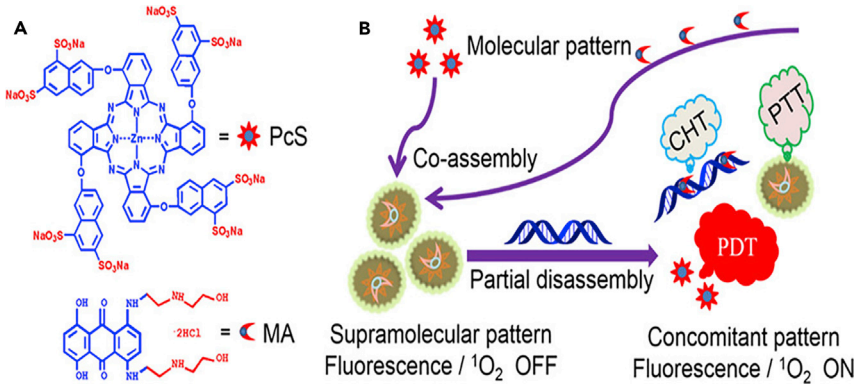

Figure 13. Nucleic-Acid-Driven Turn-On Supramolecular Theranostic Nanosystems

(A) Structures of one of the possible C4h isomers of octasulfonated phthalocyanine (PcS) and mitoxantrone (MA).

(B) Schematic illustration of the construction of a nanotheranostic agent based on supramolecular interaction between PcS and MA and its nucleic-acid-driven activatable properties for fluorescent imaging and PDT synergized with PTT and CHT.

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The results of *in vitro* studies using HeLa cancer cells showed that the dual responsive nanoparticles effectively induce cell death and apoptosis. Additionally, zebrafish larvae were used for studying the *in vivo* anti-tumor effects of the DOX-loaded nanoparticles on liver tumors. The results show that the nanoparticles improve the viability of liver tumor zebrafish larvae.

Another example using responsive nanoparticles is the fabrication of highly efficient and safe nonviral vectors. Recently, Zhu and co-workers described the construction of supramolecular gene vectors by using a supramolecular approach involving β-cyclodextrin and ferrocene host-guest recognition (Figure 14B).[90] The resultant supramolecular nanoparticles display redox-triggered reversible polymerization-depolymerization behavior alternatively triggered by H_2O_2 and GSH (Figure 14C). More interestingly, these smart nanoparticles have the ability to not only condense pDNA for efficient cell uptake but also release pDNA in the endoplasm of cancer cells.

Low-Acidity-Driven Turn-On Supramolecular Theranostic Nanosystems

Low acidity is a distinguishing feature of tumor microenvironments. This is caused by the fact that cancer cells generate large quantities of lactic acid because of their greater glycolysis and plasma membrane proton pump activities.[91] In general, the extracellular pH in tumor tissues is usually in the 6.5–6.9 range, which is lower than that in normal tissues (7.2–7.4).[92] Therefore, efforts have gone into the development of smart theranostic systems that have pH responsiveness. Li and co-workers developed cyclodextrin-derived pH-responsive nanoplatforms for the delivery of the anti-cancer drug PTX (Figure 15A).[93] The pH-responsive nanosystems were fabricated from α-CD by a one-pot procedure and then assembled into nanoparticles containing PTX. Moreover, the supramolecular nanosystems display high biocompatibility *in vitro* and *in vivo* and reverse the multidrug resistance to PTX. Furthermore, *in vivo* anti-tumor studies showed that these nanosystems possess a higher anti-tumor activity than does PTX alone.

Wang and co-workers[54] devised a pH-responsive anti-cancer drug-delivery nanosystem composed of supramolecular vesicles formed by host-guest recognition

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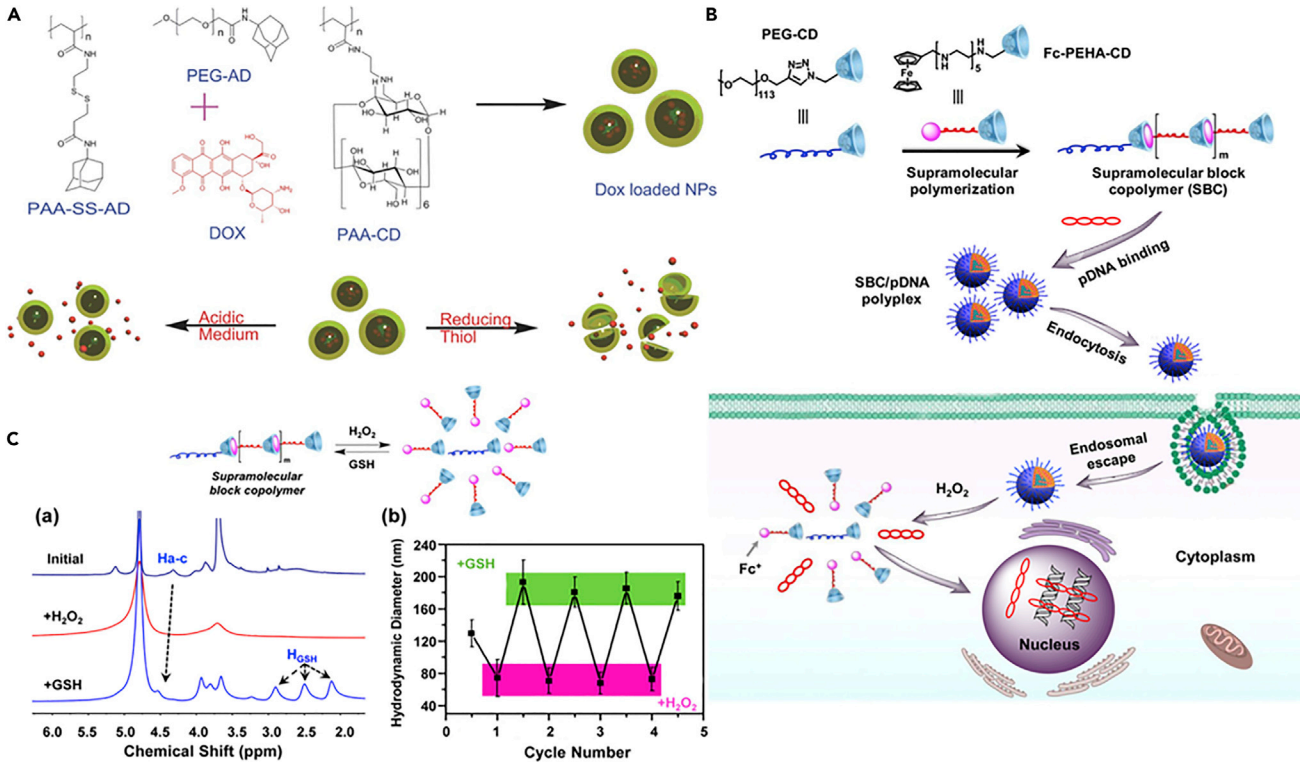

Figure 14. ROS-Driven Turn-On Supramolecular Theranostic Nanosystems

(A) Schematic illustration of the preparation of dual thiol- and pH-responsive drug-loaded supramolecular nanoparticles for *in vitro* and *in vivo* drug delivery. Reproduced with permission from Ang et al.[89] Copyright 2016 Wiley-VCH Verlag GmbH & Co. KGaA.

(B) Formation of an unconventional cationic supramolecular block copolymer and its pDNA binding and H_2O_2-triggered pDNA release *in vitro*.

(C) ^{1}H NMR spectra of SBC in D_2O at 10 mM before and after the addition of H_2O_2 and GSH (a) and periodic changes in the hydrodynamic diameter of SBC upon alternate addition of H_2O_2 and GSH (b).

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between a hydrophobic ferrocene derivative and the water-soluble pillar[6]arene (WP6) host (Figure 15B). The stable supramolecular amphiphilic host-guest complexes form in water as a consequence of the strong binding between the components and further assemble into nanosystems with controllable size (Figure 15C). Moreover, the nanosystems form MA-loaded vesicles in aqueous solution, and efficient MA release occurs when the pH of the solution is 6.0. More importantly, the cytotoxicity and cellular-uptake studies show that this nanosystem is effective for intracellular drug delivery.

ATP-Driven Turn-On Supramolecular Theranostic Nanosystems

Adenosine triphosphate (ATP) is an ideal tumor biomarker because it is much more highly overexpressed in tumor tissues (>100 μM) than in normal tissues (1–10 nM).[94] Recently, a "turn-on" tumor-targeted theranostic, which operates by biomarker displacement activation, has been developed as a dual-functioning targeted-fluorescence-imaging and PDT agent for cancer treatment. On the basis of the overexpression of ATP, Guo, Ding, and co-workers[95] devised a GCA containing binary nanocarrier that strongly encapsulates various negatively charged in its intrinsic cone-like cavity (Figure 16). The fluorescence and ROS-generating activity of the PS in this system are efficiently quenched via photoinduced electron transfer. In contrast, upon being preferentially imported in tumor cells as a result of the EPR effect, the PS is displaced from the nanoparticles by overexpressed ATP, promoting

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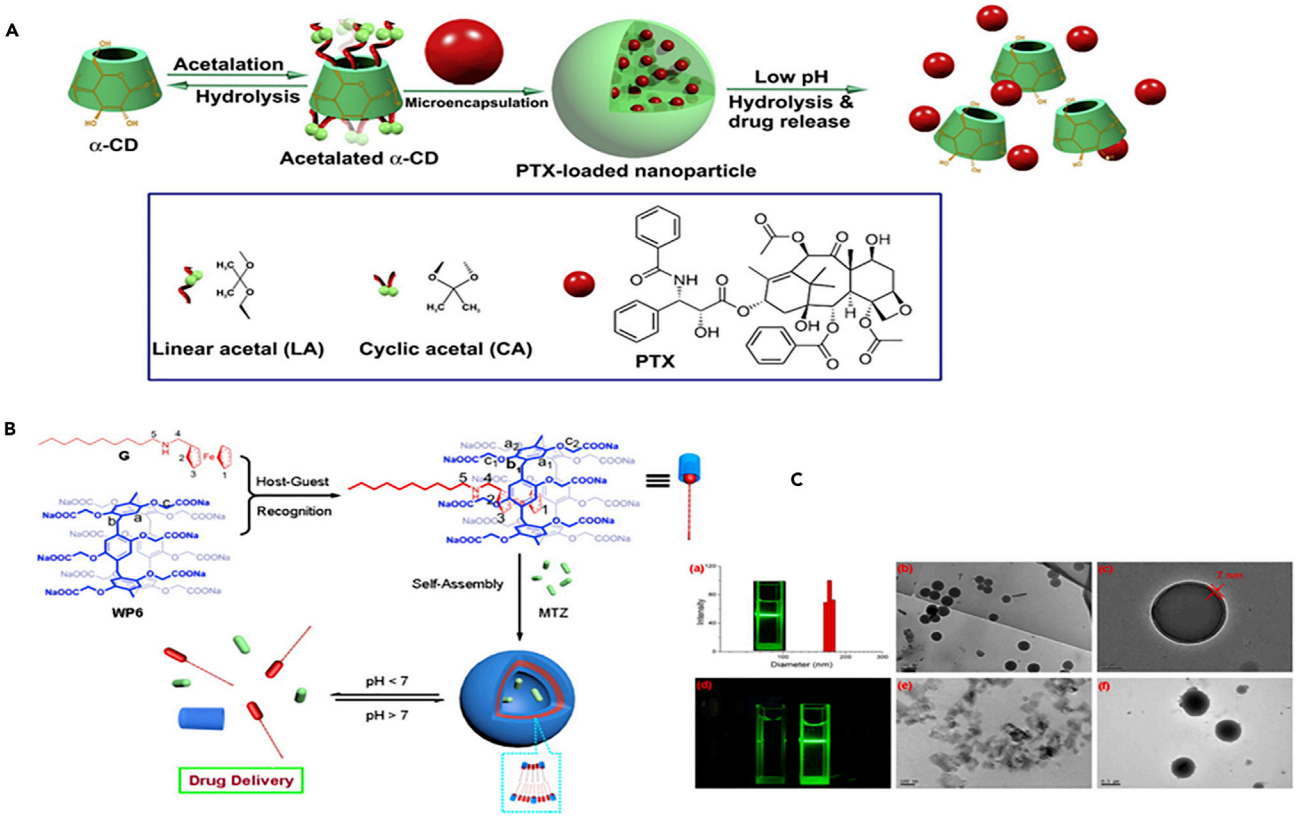

Figure 15. Low-Acidity-Driven Turn-On Supramolecular Theranostic Nanosystems

(A) Schematic illustration of the construction of pH-sensitive PTX nanoformulation based on acetalated α-CD (Ac-aCD). Reproduced with permission from He et al.[93] Copyright 2013 Elsevier.

(B) Schematic illustration of the formation of supramolecular vesicles and their pH-responsive drug release.

(C) (a) DLS data of the WP6 + G aggregates. TEM images: (b) WP6 + G aggregates and (c) enlarged image of (b). (d) Tyndall effect of WP6 + G aggregates. TEM images: (e) WP6 + G aggregates after the solution pH was adjusted to 6.0 and (f) WP6 + G aggregates after the solution pH was adjusted to 7.4.

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a return of its photoactivity and fluorescence. These effects enable real-time visualization of tumor tissues and highly efficient generation of singlet oxygen for photodynamic cancer ablation. It is believed that the biomarker displacement activation protocol can be extended to a universal strategy applicable not only to the ATP-responsive release of PSs for cancer therapy but also for the diagnostics and therapeutics of many other degenerative diseases each with its distinct target and biological trigger.

Light-Driven Turn-On Supramolecular Theranostic Nanosystems

Using light input as an external driving force for cellular events has immense advantages, such as ease of use, noninvasiveness, high spatial resolution, and temporal control.[96] Incorporation of functional chromophores, especially those that operate via photoisomerization and photochromism, into macrocycle-based nanosystems can give rise to numerous important properties.[97] In 2016, Ravoo's group developed carboxylated arylazopyrazoles as a new type of photoresponsive molecular switch.[98] Superior to the conventional nanosystems utilizing azobenzenes, those containing water-soluble arylazopyrazoles display more effective switching behaviors in the presence of β-CD.[99] Another example demonstrating the utility of arylazopyrazoles is found in their use in manipulating biomacromolecular aggregation behavior.

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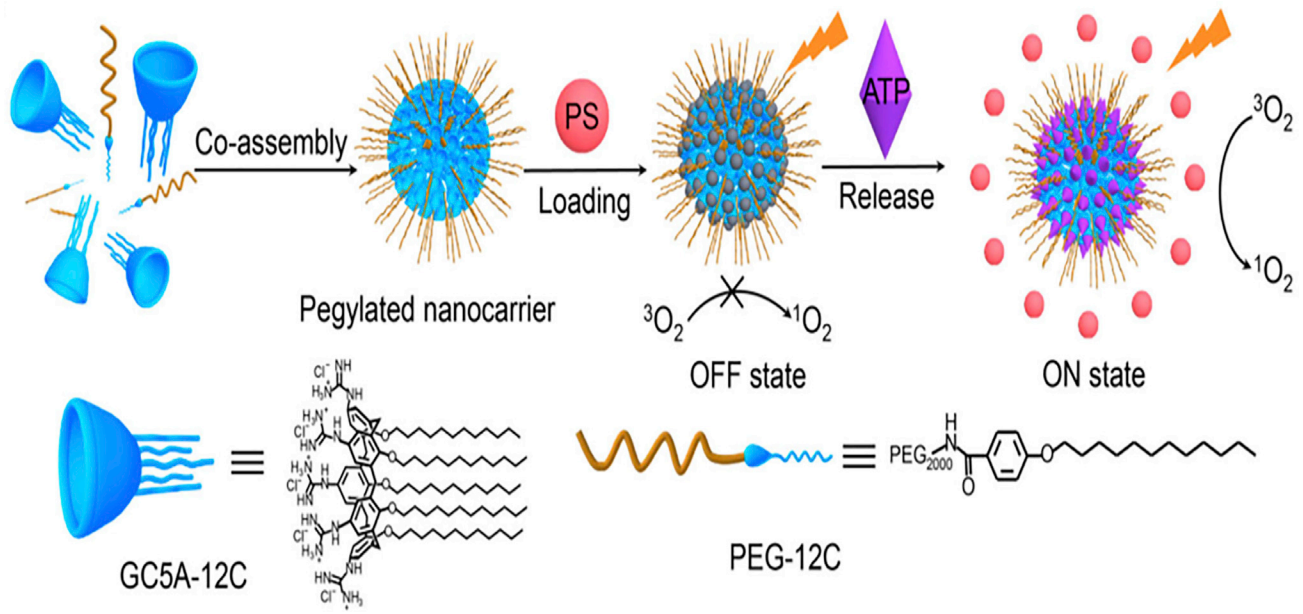

Figure 16. Schematic Illustration of the Pegylated GC5A-12C Nanocarrier for Biomarker Displacement Activation, where the Fluorescence and Photoactivity of PS Are Annihilated by the Complexation of GC5A-12C and Reactivated by ATP Displacement
Reprinted with permission from Gao et al.[95] Copyright 2018 American Chemical Society.

Recently, Liu and co-workers described a novel strategy for constructing a photocontrolled supramolecular assembly based on the complex formation between naturally occurring microtubules and artificial macrocyclic receptors (Figure 17A).[100] This reversible complexation process was achieved with a PTX-modified β-CD and an arylazopyrazole as host and guest molecules, respectively. The results of an investigation using spectroscopic and microscopic methods showed that intertubular aggregation of microtubules in this system can be reversibly regulated by photoisomerization of the arylazopyrazole group and that the change is accompanied by dramatic morphological changes. Significantly, this CD-mediated photoswitchable aggregation process occurs in selected cellular environments where it results in serious cell shrinkage and death (Figure 17B).

Furthermore, most macrocyclic receptors have biocompatible hydrophobic microenvironments that preserve and even improve the photochemical properties of phototherapeutic agents in a way that benefits photoactivated cancer theranostics. For instance, host-guest complexation with PEGylated CA[4] prevents fluorescence self-quenching of the hydrophobic PDT PS chlorin e6, and it facilitates the formation of supramolecular polymeric micelles that are suitable for passive delivery into target cells, leading to high cellular uptake and photodynamic efficacy in cancer cells.[101] In another example, fluorescence emission and singlet oxygen generation of a pyridinium-bearing porphyrin derivative are largely recovered upon its complexation with CB[7], leading to a dramatic enhancement in anti-bacterial activity compared with that of the unbound porphyrin.[102] A similar strategy was utilized for *in vivo* bioimaging. In this case, α-CD-threading polypseudorotaxanes were introduced into the outer surface of upconversion nanoparticles, making them useful as a contrast agent for *in vivo* photoacoustic imaging.[103] Benefiting from complexation-assisted phase transfer from organic to aqueous media, the resultant nanoparticles possess high dispersibility, quenched luminescence, increased thermal conductivity, and enhanced photoacoustic signal production upon 980 nm excitation.

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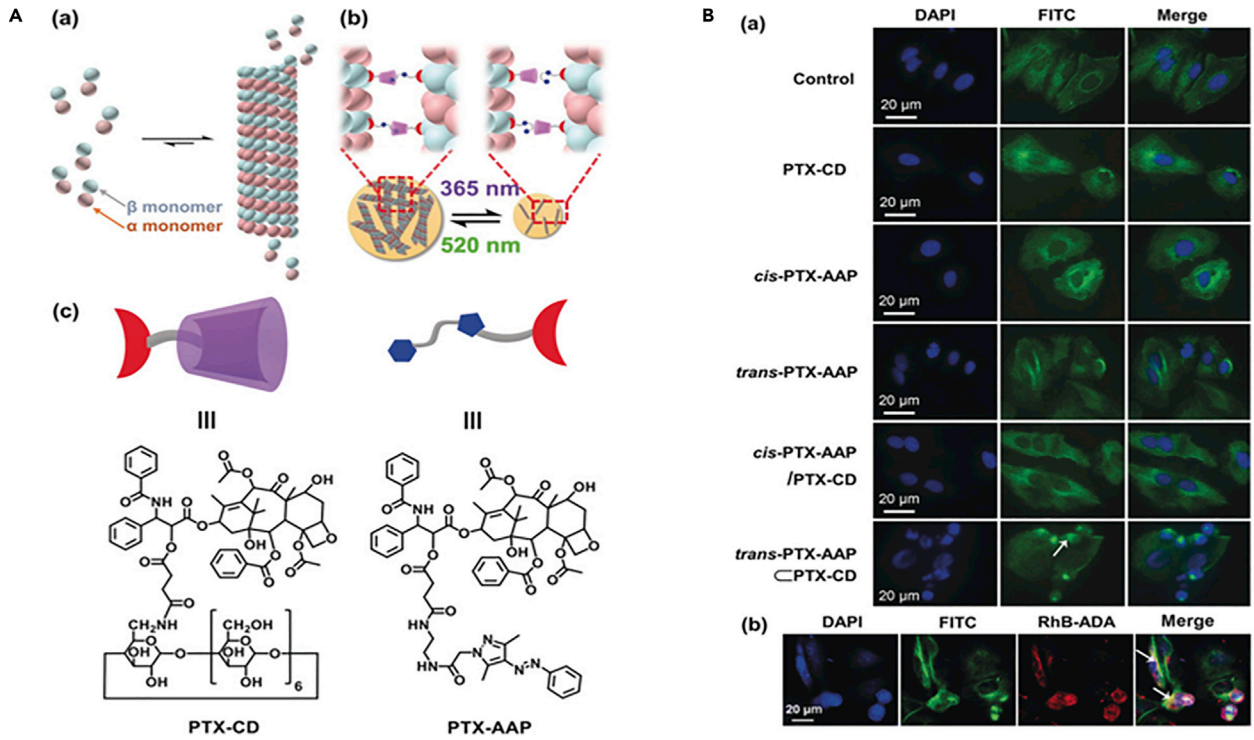

Figure 17. Light-Driven Turn-On Supramolecular Theranostic Nanosystems

(A) Schematic and structures of (PTX-AAP⊂PTX-CD) @MT ternary supramolecular assembly.

(B) Confocal microscope images of the A549 cell line after treatment with PTX-CD, PTX-AAP, and their corresponding complexes (a) and co-localization of aggregated MTs and the *trans*-PTX-AAP⊂PTX-CD complex (b). DAPI was used to stain the nucleus. Typical compact MTs are indicated by white arrows. Reprinted with permission from Zhang et al.[100] Copyright 2018 Wiley-VCH Verlag GmbH & Co. KGaA.

CONCLUSIONS AND PERSPECTIVES

Supramolecular host-guest based nanosystems used as theranostics have received widespread attention in biomedicine. As described above, various types of cancer-associated, turn-on supramolecular host-guest nanosystems have been shown to be superior as theranostics for cancer diagnosis and treatment. As a specific sub-class of supramolecular platforms, host-guest nanosystems are formed through the association between functional guest molecules and host macrocycles, including cyclodextrins, calixarenes, cucurbiturils, pillararenes, and Pcs. In this review, we summarized recent progress made in the design of turn-on supramolecular theranostic nanosystems whose activities are triggered by glutathione, polyamines, specific proteins, nucleic acids, ROS, slight acidity, ATP, and light.

Although significant progress has been made in designing new supramolecular theranostic nanosystems, several problems and challenges still exist. For example, premature release of loaded drugs before reaching target cells often limits the use of these nanosystems for drug delivery because of serious issues arising from severe effects on normal tissues. Therefore, the development of supramolecular nanosystems that are extremely stable during blood circulation and are triggered exclusively in cancer cells remains a challenge. To reduce side effects and enhance anti-cancer drug efficacy, the selectivity of supramolecular nanosystems for cancer cells needs to be improved, perhaps by employing multiple targeting ligands. In addition, reducing the toxicity of nanocarriers and enhancing their biodegradability is required for use of these systems for the treatment of real patients. Taking into

account the innovations made thus far, we believe that new supramolecular nanosystems strategies for addressing all these challenges will be developed in the near future.

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AUTHOR CONTRIBUTIONS

J.Y. and Y.L. proposed the topic of the review. H.C. and Y.Z. investigated the literature and wrote the original manuscript. All authors read, revised, and approved the manuscript. H.C. and Y.Z. contributed equally to this work.

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