Cyclodextrin-Based Multistimuli-Responsive Supramolecular Assemblies and Their Biological Functions

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Cyclodextrins (CDs), which are a class of cyclic oligosaccharides extracted from the enzymatic degradation of starch, are often utilized in molecular recognition and assembly constructs, primarily via host–guest interactions in water. In this review, recent progress in CD-based supramolecular nanoassemblies that are sensitive to chemical, biological, and physical stimuli is updated and reviewed, and intriguing examples of the biological functions of these nanoassemblies are presented, including pH- and redox-responsive drug and gene delivery, enzyme-activated specific cargo release, photoswitchable morphological interconversion, microtubular aggregation, and cell–cell communication, as well as a geomagnetism-controlled nano-system for the suppression of tumor invasion and metastasis. Moreover, future perspectives and challenges in the fabrication of intelligent CD-based biofunctional materials are also discussed at the end of this review, which is expected to promote the translational development of these nanomaterials in the biomedical field.

1. Introduction

Cyclodextrins (CDs), which were discovered incidentally by Antoine Villiers in 1891 as a by-product of fermentation-mediated carbohydrate degradation, are a family of truncated cone-like macrocyclic oligosaccharides connected by α-1,4-glucosidic bonds.[1] In terms of the number of α-glucose units, native CDs can be classified as α-, β-, and γ-CDs, which can be now synthesized via large-scale industrial production (Figure 1a). During the past 120 years of development, especially the rapid progress made since the 1980s, a large number of pioneers and luminaries have left their mark on the history of these fascinating molecules and greatly promoted their practical applications in nearly all aspects of industry.[2] In the academic field, CD-based molecular recognition and assembly have become a focus of interest in supramolecular chemistry during the last few decades, primarily due to their superior molecular binding abilities toward various organic and bioactive substrates in both aqueous solution and solid states.[3] Furthermore, many molecular-scale nanostructures with unique topological features, such as catenanes, (pseudo)rotaxanes, supramolecular polymers, cross-linked hydrogels and networks, and functionalized nanoparticles, can be derived from the self-assembly of CDs, which have greatly expanded the research objectives for supramolecular chemistry (Figure 1b–g).[4]

Nanosized stimuli-responsive materials can adapt to microenvironmental variations and respond in a dynamic manner, thereby providing an efficient way to mimic the responsiveness of natural and physiological processes.[5] This strategy can further enable us to fabricate intelligent nanomedicine, nanotherapeutics, and biomimetic nanomaterials.[6] Moreover, the choice of an ideal stimulus that functions in a biological system requires the consideration of several factors, such as biocompatibility, intended sites of action, and safety concerns. In this regard, CD units are believed to be one of the most useful building blocks for the construction of stimuli-responsive supramolecular assemblies because they exhibit a good size/shape matching ability upon binding of guest molecules based on the dynamic and reversible nature of noncovalent interactions. Thus, the covalent or noncovalent introduction of stimuli-responsive sites into CD moieties can be viewed as a feasible means of conferring smart chemistry to rigidified macrocyclic receptors that lack environmentally responsive characteristics.[7]

In the following sections, we will highlight the most recent achievements in the realm of CD-based multistimuli-responsive nanoassemblies, with an emphasis on their biological functions in reversal of cytotoxicity, delivery and release of therapeutic agents, and combinational cancer therapy. We also focus on the commonly used stimuli-sensitive components in CD chemistry that allow one to tune the physicochemical properties and intermolecular aggregation in a controlled fashion. The synthetic strategies, molecular binding modes, and structure–activity relationships in response to classic internal and external stimuli are systematically reviewed. Although more exciting developments are still being investigated, the examples presented herein clearly demonstrate the numerous opportunities and practical applications that can stem from the diversity and complexity of CD-based stimuli-responsive nanosystems.

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Due to limited space, it is not possible for us to review all the works in this increasingly significant field; thus, we only selected certain exciting and inspiring systems that exemplify delicate molecular design and potential biological applications based on our own experience. We believe that the biocompatible nanoassemblies described in this review are just the tip of the iceberg. With the revolutionary advances in material science and nano- and biotechnology, many new types of CD-based stimuli-responsive supramolecular assemblies with high controllability and appealing functions can be imagined in the future.

2. pH-Responsive Supramolecular Assemblies

The pH sensitivity of CD-based supramolecular assemblies is a crucial concern for the successful implementation of these assemblies in biomedical fields. Cellular compartments, body fluids, and organs all have their own characteristic pH values that maintain acid–base homeostasis, which enables us to construct pH-sensitive supramolecular assemblies that can be specially localized at intended sites of action. In addition, abnormal pH values can be identified as risk factors for physiological dysfunction and disease. Particularly, due to the overproduction of acidic metabolites under oxygen- and nutrient-deprived environments, the pH value of the tumor environment (≈6.8) is slightly lower than that of normal tissues (≈7.4). Therefore, CD-based supramolecular nanocarriers susceptible to an acidic environment can discriminate tumor cells from normal cells, thus facilitating the targeted and reliable delivery and release of therapeutic drugs for potential clinical use. More importantly, supramolecular nanosystems working in a broad range of pH variations can provide theoretical models to stimulate drug capture and release in organs with different pH environments, such as the stomach and intestine.[8]

2.1. pH-Sensitive Linkages

Many acid-labile substituent groups, such as cis-aconityl spacer, hydrazine,[9] oxime, acetal,[10] and ketal groups,[11] as well as histidine and imidazole, have been widely employed to construct pH-sensitive nanosystems for biological application. In particular, on account of the structural characteristics of CDs, which have multiple α-glucose units, the dynamic covalent bonds between boronic acids and diol compounds are often incorporated into CD-based nanosystems to construct supramolecular self-healing materials[12] and drug delivery systems.[13] An interesting work presented a dual pH-responsive supramolecular hydrogel formed by host–guest interaction, that is, the polyethylene glycol (PEG) chain and the anticancer drug doxorubicin were covalently introduced into the polyphosphoester backbone via acetal and hydrazone linkers, respectively, thus conferring pH-sensitivity to the polymeric nanomedicine (Figure 2a).[14] Interestingly, a prodrug-loaded supramolecular hydrogel, which might be applied as an injectable drug delivery system, was readily formed by the threading of α-CDs onto PEG side chains.

Furthermore, the controlled delivery of biomacromolecules and drug molecules has been greatly enhanced by the development of functionalized nanomaterials equipped with zwitterionic and charge-reversal sites.[15] Zwitterionic nanocarriers contain both positive and negative charges connected in the same monomeric or polymeric skeleton,[16] whereas charge-reversal nanocarriers specifically refer to carriers that can retain a negatively charged surface under physiological conditions but instantly convert to a positive charge at lower pH values.[17] These biocompatible materials are the two main types of pH-driven transformable agents with the capacity to adapt to the external acid–base environment, thus making them more suitable for gene delivery and cancer therapy. For example, a binary supramolecular nanoparticle was constructed by inclusion complexion between β-CD-grafted hyaluronic acid (HACD) and an adamantane derivative bearing two ammonium tails, which could tightly bind plasmid DNA via electrostatic interactions (Figure 2b).[18] When the ethyl ester bonds on the guest molecule were hydrolyzed to carboxyl groups, a zwitterionic
structure was formed to decrease the cationic density, and the condensed DNA was accordingly released under basic conditions. The pH-sensitive charge-reversal strategy can also be applied in multimodal tumor therapy. In a recent study, Cai and co-workers reported a multifunctional nanoplatform based on a β-CD-coated silica–gold hybrid nanorod for combined photodynamic–photothermal cancer ablation therapy (Figure 2c). [19] The electrostatic mask of an adamantane-modified mitochondria-targeting peptide with 2,3-dimethylmaleic anhydride-protected chitosan endowed the nanoassembly with the desired stealth property, thus facilitating cellular internalization at the tumor site via the enhanced permeability and retention effect. Moreover, amide bonds were cleaved to deshield the positively charged amino groups under the mildly acidic intracellular microenvironment, and the removal of the chitosan oligosaccharide shells led to specific accumulation in mitochondria in an electrostatic repulsion–dependent manner. The resulting improved therapeutic efficacy in a mouse model was attributed to the augmented generation of reactive oxygen species and enhanced local hyperthermia.

### 2.2. Protonatable Sites

The introduction of basic guests with protonatable nitrogen atoms into the CD skeleton is another feasible strategy to attain pH-sensitive nanoassemblies. Early studies revealed that the molecular recognition process of pyridyl group-bridged bis(β-CD) with oligopeptides and steroids was profoundly influenced by changes in the pH value of an aqueous solution. [20] Moreover, among the frequently encountered organic amines and nitrogen-containing heterocycles, N-alkylated benzimidazoles possessing the appropriate π-aromatic conjugation and molecular size can undergo reversible association–disassociation processes with the cavity of β-CD because CDs as anion-receptor hosts have distinct binding abilities toward protonated and neutral benzimidazoles upon alternating additions of acids and bases. According to a pKₐ analysis, N-methylbenzimidazole (pKₐ = 5.67) is the best candidate and can be protonated to a large extent in endosomal compartments (pH < 6). [21] Recently, Yuan and co-workers wrote an excellent review discussing drug delivery systems based on the inclusion complexation between CDs and benzimidazole with pH and CO₂ sensitivity. [22] In a more recent study, Yu and co-workers constructed a multifunctional drug delivery system using inclusion complexation between benzimidazole-grafted mesoporous silica nanoparticles and β-CD-modified CuS nanoparticles that showed rapid drug release after the benzimidazole moiety was protonated in an acidic tumoral environment (Figure 3a). [23] This organic–inorganic hybrid nanocarrier exhibited a synergistic antitumor effect at the cellular level via combined chemotherapy and photothermal therapy activities. Furthermore, the protonation of aliphatic amine-modified CDs is also utilized for pH-activated drug release and delivery. For instance, a pH-responsive nanosystem for succinobucol was constructed utilizing the host–guest interaction between PEGylated adamantane and a hydrophobic β-CD derivative appended with multiple amino arms at its narrow rim. This system showed satisfactory suppression of lung metastasis in breast cancer (Figure 3b). [24] Specific drug release in response to the slightly acidic environment inside the cancer cells was achieved as soon as the hydrophilic–hydrophobic balance of the obtained spherical nanoparticles was disrupted by the protonation of the tertiary amino groups in the host compound.

### 2.3. Optimization of CD-Based Bioactive Assemblies via pKₐ Regulation

The acidity constant (pKₐ) can directly reflect the protonation state in solution, and the specific structure–activity relationship of a given chemical group is largely dependent on its state of protonation. Precise control over protonation–deprotonation equilibrium can facilitate the primary electrostatic stabilization of native biomacromolecules, by which some secondary non-covalent interactions can be stimulated and diverse biological functions can eventually be achieved in many physiological events. In this section, we will illustrate how the pKₐ values of
host and guest molecules affect the biological activity of CD-based supramolecular assemblies.

One example of this process comes from the inhibition and reversal of the cytotoxicity of deoxycholic acid (DCA) by supramolecular encapsulation (Figure 4a). It is known that CDs are capable of forming stable host–guest complexes with various lipophilic molecules, and the physiologically important bile acids are frequently used as the ideal model guests in CD chemistry. However, there is a serious bottleneck in exploring the biological significance and practical application of bile acid–CD supramolecular systems.

Previously, Liu and coworkers found that d-tyrosine-modified β-CD could greatly enhance the molecular binding ability and selectivity toward bile acids. Motivated by this work, an optimized system...
involving tyramine-modified β-CD was reported by the same group, and the molecular binding strength in this CD-based molecular recognition was largely improved by decarboxylation of tyrosine to form tyramine. Quantitative pH-analyses revealed that under physiological conditions (pH 7.20), the singly charged form with a protonated amino group was the predominant species of tyramine-modified β-CD (92%, \( pK_a,1 \approx 8.27 \) and \( pK_a,2 \approx 9.20 \)), but \( \sigma \)-tyrosine-modified β-CD exclusively presented as the zwitterionic form (99%, \( pK_a,1 \approx 2.65, pK_a,2 \approx 9.11, \) and \( pK_a,3 \approx 9.62 \)). Therefore, lacking the carboxyl group, the tyramine-modified β-CD could tightly bind bile acids through the cooperativity of electrostatic and hydrophobic interactions. Next, the obtained tyramine-modified β-CD was applied in the clearance of bile acids both in vitro and in vivo to address the toxic and adverse effects of long-term intracellular accumulation of endogenous bile acids. Compared with the native and tyrosine-modified β-CDs, the tyramine-modified β-CD exerted an improved protective effect against DCA-induced cytotoxicity, and cellular viability could largely be recovered upon incubation with tyramine-modified β-CD. Furthermore, the excess DCA could be rapidly cleared through urinary excretion, thus maintaining the concentration of total bile acids at a normal level in the mouse blood.

The other example is related to the targeted delivery of siRNA by a supramolecular \( pK_a \) shift (Figure 4b). Recent studies have demonstrated that macrocyclic encapsulation...
is a sturdy tool that alters the chemical and biological activities of included guests through the complexation-induced $pK_a$ shift strategy.\[29\] It is known that different types of macrocyclic receptors have different impacts on the variation of $pK_a$ values; for example, positive $pK_a$ shifts are frequently observed upon the complexation of weakly basic guests with cucurbiturils, while negative shifts are always expected for cyclodextrins. In this case, a water-soluble ammonium salt consisting of one adamantane head and two butanediamine tails was found to form a stable inclusion complex with two cucurbit[6]urils, and the noncovalent decoration of HACD with the exposed adamantyl groups could further endow the resultant supramolecular nanoparticles with the ability to selectively transport nucleic acids into cancer cells via receptor-mediated internalization. Significantly, there were large positive shifts for the amino groups of the guest molecule in the presence of cucurbit[6]uril ($\Delta pK_{a,1} = 1.1$ and $\Delta pK_{a,2} = 1.0$); thus, at pH 7.20, the species distribution of doubly protonated guests increased from 58% to 95%, while that of singly protonated guests decreased from 41% to 5% before and after complexation with cucurbit[6]uril, respectively. Therefore, the density of positive charges in neutral aqueous solution was dramatically enhanced with the assistance of cucurbit[6]uril, which could be responsible for the improved siRNA-condensing ability, efficient uptake by malignant cells, and high gene transfection efficacy.

3. Redox-Responsive CD-Based Supramolecular Assemblies

Given the different charge potentials and redox states widely distributed in the intra/extracellular environments, considerable endeavors have been devoted to exploring biocompatible nanoarchitectures possessing redox-sensitive groups for stimuli-responsivity to specific sites. In this regard, the reduction-sensitive disulfide bond and electroactive ferrocenyl group are frequently utilized in the fabrication of CD-based redox-responsive supramolecular systems because the former can be selectively cleaved to free thiols in the presence of internal bioreducing thiol agents, such as glutathione (GSH), to achieve targeted drug release at the desired location,\[30\] whereas the latter can be reversibly encapsulated in and expelled from the $\beta$-CD cavity in a single-electron oxidation and reduction process.\[31\]

3.1. Disulfide-Bond Linkage

In this respect, in addition to the conventional disulfide-linked CDs used to achieve host-guest complexation,\[12\] it has been realized that many CD-derived topologically interesting nanostructures, including (pseudo)polyrotaxanes and supramolecular polymers, can be actively exploited in the design of
functional biomaterials. Previously, cationic CD-based polyrotaxanes were mainly used as nonviral vectors for the transfection of mammalian cells with polynucleotides. Presently, more stimuli-cleavable polyrotaxanes have been rationally designed as a technically feasible strategy for therapeutic applications.

For example, Yui and co-workers constructed a type of 2-hydroxypropyl β-CD-threaded polyrotaxane containing reduction-cleavable disulfide-bond linkages that exhibited a clear cholesterol-reducing effect for the treatment of Niemann–Pick type C disease.

Very recently, new research findings have demonstrated that polyrotaxane-based supramolecular assemblies with a disulfide linkage can be developed as multifunctional nanocarriers for cancer diagnostics and therapeutics. Thus, multicomponent nanoparticles were elaborately fabricated by the self-organization of CD-based polyrotaxanes using perylene diimide and the RGD (Arg-Gly-Asp) peptide sequence to decorate the terminal ends (Figure 5a).[36] The hydrophobic drugs paclitaxel (PTX) and camptothecin (CPT) could be concurrently loaded inside the supramolecular nanoparticles. The pristine nanoparticles were then tightly sealed by a condensation reaction between amino-substituted β-CD and disulfide bond-containing crosslinkers to avoid unfavorable premature drug leakage. Benefiting from mutual cooperativity between targeting localization and photoacoustic imaging, as well as synergistic chemotherapy–photodynamic therapy, the resultant shell-cross-linked nanoparticles exhibited a satisfactory curative effect on breast cancer, which may pave a new path for safe and effective cancer treatment using supramolecular nanomedicines.

In subsequent work, this team reported a polyrotaxane-based theranostic nanosystem formed by the self-exclusion complexation of CPT-modified β-CDs containing cleavable disulfide bonds (Figure 5b).[37] The supramolecular polymerization dramatically increased the water-solubility of CPT and prevented it from an unfavorable ring-opening deactivation. Then, the stable multicomponent nanoparticles were formed through the orthogonal self-assembly of 1D polymeric rotaxanes. Furthermore, the targeting ligand and imaging agent could be conveniently integrated into the outer surface via noncovalent modification. As a result, the obtained hierarchically self-organized supramolecular nanomedicine could be specifically delivered to GSH-overexpressing tumor cells and exerted enhanced anticancer activity and ant Metastasis effects with rather low systemic toxicity. This work further emphasizes the dynamic nature of supramolecular nanoassemblies in overcoming the physiological drawbacks of parent drugs and minimizing the adverse effects of traditional chemotherapeutics.

3.2. Ferrocenyl Group

In addition to the CD-based nanoassemblies, ferrocene is an ideal redox-sensitive group that possesses good size/shape matching with many other macromolecular receptors, such as cucurbiturils[38] and pillararenes.[19] Ferrocenyl-containing polymeric and supramolecular nanosystems have been extensively studied, especially for controlled capture and release, primarily due to their dynamic redox switching behavior that can be conveniently regulated by a chemical or electrochemical stimulus. In addition, in view of the reversible association and disassociation in response to external redox signals, ferrocene–CD conjugates have been actively developed as versatile chemical sensing systems for fast and selective monitoring of various analytes in bioassays,[40] such as small bioactive molecules,[41] nucleic acids,[42] antigens,[43] proteins,[44] and bacteria.[45]

As an important biological hallmark, hydrogen peroxide ($\text{H}_2\text{O}_2$) is considered the optimal stimulus in ferrocene-involved anticancer systems because the concentration of $\text{H}_2\text{O}_2$ at tumor sites is intrinsically higher than that at normal sites. With a clear understanding of these seductive properties, Dong
and co-workers reported a new type of supramolecular block copolymer, in which the supramolecular self-polymerization of ferrocene-modified β-CDs was terminated by PEGylated β-CD (Figure 6a). This cationic supramolecular polymer could be used as a gene vector to form a stable polyplex with plasmid DNA via electrostatic interaction; then, the DNA could be readily released inside cells to achieve superior gene transfer efficacy after the neutral ferrocene was oxidized to its corresponding ferricinium form by H₂O₂. Another successful example comes from ferrocene-promoted oxidation therapy. Thus, a multifunctional polymeric nanoparticulate system was constructed by coassembling a β-CD-grafted diblock copolymer with ferrocene and ascorbyl palmitate. Intriguingly, a two-step consecutive chemical reaction occurred in tumor cells, thereby permitting the conversion of H₂O₂ into a highly cytotoxic hydroxyl radical via the ferrocene-catalyzed Fenton reaction. As a result, tumor growth was largely suppressed after intravenous injection of the ternary integrated micellar nanoparticles. A simple and good example of a dual redox-responsive supramolecular nanoassembly with a significant inhibition effect on cellular proliferation and tumor growth is a polymer-drug conjugate constructed by the inclusion complexation between PEGylated β-CD and ferrocene-modified CPT linked by a disulfide bond (Figure 6b). The obtained binary supramolecular micelles showed hyperfast redox-responsive drug release behavior in the presence of GSH and H₂O₂, which was attributed to the chemical reduction of the disulfide bond and chemical oxidation of the ferrocenyl group, respectively.

4. Enzyme-Responsive CD-Based Supramolecular Assemblies

On one hand, as a type of enzymatically hydrolyzed starch used for a diverse range of practical applications, CDs are closely related to cyclodextrin glycosyl transferases; on the other hand, the intrinsically hydrophobic cavities of CDs have long been exploited as ideal models to mimic the substrate-binding pockets of naturally occurring enzymes. Recently, considerable research effort has been made to introduce enzyme-responsive sites into CD-involved supramolecular assemblies, in which specific disease-associated enzymes can be utilized as desirable targets for diagnostic and therapeutic purposes. Furthermore, a variety of enzyme-triggered assembly and disassembly modes, including the recovery of a disulfide bond by horseradish peroxidase, disruption of protamine by trypsin, cleavage of benzoquinone and azobenzene by oxidoreductase, rupture of myristoylcholine chloride by butyrylcholinesterase and destruction of a specific polypeptide sequence by cathepsin B, have been extensively utilized in the construction of smart CD-based supramolecular nanoassemblies with broad bioanalytical and biomedical applications.

In this context, the biodegradation of CD glucose bonds by α-amylase has been developed as a direct and general approach to construct biocompatible enzyme-responsive nanomaterials. For example, surfactant molecules can be released from CD cavities in the presence of α-amylase, thereby triggering the formation of diverse morphologically interesting aggregates ranging from monolayers to micelles and vesicles. This strategy was further applied in tuning the photophysical behaviors of bolaform amphiphiles (Figure 7a). In this case, the fluorescence emission of naphthalene-bridged bispyridinium salt was greatly enhanced by inclusion complexation with β-CD, while it was gradually quenched upon the addition of α-amylase. More gratifyingly, the enzymatic activity could be quantitatively determined by virtue of a linear correlation between the concentration of α-amylase and the initial rate of fluorescence quenching. Therefore, it is reasonable to assume that this study provides a practical platform for the diagnosis of α-amylase-associated diseases, such as acute pancreatitis. Moreover, for a better potential application, He and co-workers recently constructed...
an α-CD-capped hollow mesoporous silica nanoparticle that exhibited an extraordinarily high loading ability and controlled release behavior toward chlorantraniliprole (Figure 7b). This pesticide-loaded nanosystem also showed good stability under thermal and UV stresses and provided satisfactory insecticidal activity and remarkable persistence after treatment with exogenous α-amylase compared with a commercial formulation. Given that α-amylase is widely present in the midgut and salivary glands of larvae with chewing mouthparts, this nanosystem with a controlled release formulation is quite suitable for the on-command delivery of active ingredients in agricultural pest control.

Furthermore, an impressive advance in CD-based enzyme-responsive nanosystems is the combination of CD with bio-compatible hyaluronic acid (HA). In the past few years, inventive applications for HA–CD nanosystems have been found in miscellaneous fields, such as tissue engineering and regenerative medicine, as well as in the manufacturing of biomimetic materials with tunable rheological properties. For cancer therapy applications, decoration with an HA shell can not only solubilize and stabilize theranostic payloads via multiple cooperative interactions but also confer the desired targeting ability on CD-based supramolecular nanoassemblies. More importantly, after specific localization via receptor-mediated endocytosis, the expeditious release of therapeutic drugs can be further achieved by specific hyaluronidase-triggered degradation in cancer cells. For example, Liu and coworkers reported a targeted polysaccharide nanoparticle based on the hydrophobic encapsulation of an adamantyl prodrug with HACD, thus leading to a comparable curative effect but a much lower toxicity than the free drug. It was also demonstrated that the obtained nanoparticulate assemblies could be completely disassembled after the endo-N-acetylhexosaminic bonds in the HA chains were hydrolyzed to low-molecular-weight oligomeric segments upon the addition of hyaluronidase. Similarly, a theranostic nanoplatform was constructed from tirapazamine-loaded mesoporous silica nanoparticles, followed by layer-by-layer coating with permethyl CD-grafted HA and gadolinium (III)-coordinated porphyrin sulfonate through host–guest complexation. With the assistance of in vivo near-infrared fluorescence and magnetic resonance imaging guidance, the combined photodynamic–chemotherapy of tumors could be concurrently achieved when the versatile nanoassemblies were specifically dissipated by the overexpressed hyaluronidase in cancer cells.

As described above, it is clear that CD-based enzyme-responsive nanoassemblies are still in their earliest stages of development and there are limitless possibilities in this promising field. Taking advantage of the facile chemical modification and intermolecular inclusion complexation, we anticipate that many known CD derivatives and newly synthesized CDs will be endowed with exceptional biorecognition capability, which may facilitate the targeting of a specific site by the programmed enzymatic digestion of nanocarriers. Moreover, since numerous diseases are characterized by dysregulation and an imbalance in enzymatic expression and activity, CD-based ultrasensitive biosensors can be elaborately fabricated for chemical analysis and disease diagnostics.

5. Photoresponsive Supramolecular Assemblies

By virtue of light input as a noninvasive and eco-friendly stimulus, photosensitive supramolecular assemblies may hold great promise for the treatment of many life-threatening diseases and intoxications, as recently exemplified by the cucurbit[8]uril-derived photoswitchable user-friendly
Among the frequently encountered photoisomeric molecules, azobenzene and its water-soluble derivatives are regarded as ideal candidates for the construction of CD-based photoresponsive supramolecular nanarchitectures because they exhibit strikingly distinctive binding affinities with the α-CD cavity upon reversible trans- and cis-photoisomerization (Figure 8a, I). Specifically, the stability constant for the trans-azobenzencα-CD complexation is estimated as 2000 M⁻¹, whereas this value sharply decreases to only 35 M⁻¹ for cis-azobenzencα-CD complexation in aqueous media upon exposure to UV irradiation.⁶⁷ This large disparity in binding strength provides researchers with bountiful opportunities for remote and reversible control over morphological conversion,⁶⁸ phase transition,⁶⁹ wetting behavior in nanochannels,⁷⁰ optical and chiroptical properties,⁷¹ catalytic performance of natural enzymes,⁷² and inhibition of cytotoxicity,⁷³ as well as the capture and release of drug molecules,⁷⁴ nucleic acids,⁷⁵ proteins,⁷⁶ and even bacteria.⁷⁷ More importantly, the near-infrared photoswitching of CD-containing complexes can be achieved via the photon upconversion mechanism, which would further ensure the ease of operability of photochromic azo-compounds in biological environments.⁷⁸

Furthermore, this supramolecular strategy based on azobenzencCD complexation has been successfully implemented in the spatiotemporal regulation of cell–cell communication and in situ bioorthogonal catalysis. Thus, using a combination of metabolic glycan labeling and a Cu(I)-catalyzed cyclization reaction, β-CD units were conveniently introduced onto cell membranes (Figure 8b).⁷⁹ Thus, cell-surface noncovalent modification with fluorescent dye, cell adhesion and release on a patterned substrate, and intercellular contact could be reversibly controlled by photoresponsive assembly and disassembly behaviors between β-CD and azobenzene. In a recent study, the same group reported the light-gated control of bioorthogonal catalysis by Pd⁰ nanoparticle-embedded and azobenzene-modified macroporous silica nanoparticles.⁸⁰ The inhibition and recovery of the catalytic activity could be reversibly regulated by the capping and decapping of β-CD with azophenyl groups, and the controlled catalytic performance of this nanosystem was verified by Pd-catalyzed deallylation and cross-coupling reactions as well as by the activation of a produg in living cells (Figure 8c).

As for light-operated delivery nanoplatforms, a representative achievement comes from the smart combination of mesoporous silica nanoparticles and stimulus-responsive mechanically interlocked molecules, such as macrocycle-based (pseudo)rotaxanes.⁸¹ For instance, α-CD was readily accommodated at the azophenyl center, and an adamantyl group was used as a stopper to hold back the detreading of a CD unit from a molecular axle. Initially, no dye molecules could escape from the pore openings because of the high binding affinity between α-CD and trans-azobenzene.⁸₂ Then, α-CD was forced to move toward the adamantyl terminal of the stalk when exposed to UV light, followed by the successive release of cargos from the silica nanoparticles. This release and entrapment process could be reversibly regulated by light irradiation and thermal relaxation. Interestingly, the loading of cargo molecules was selectively dependent on the molecular size of the entrapped fluorophores and the stalk length of the azophenyl axle. These (pseudo)rotaxane-based nanovalves responsive to an external light source may hold great promise for targeted and light-activated intracellular drug delivery. Moreover, in view of the rapid, directional, and noninvasive characteristics of photoresponsive supramolecular systems, researchers have diverted their attention toward new ways to transport dye and drug molecules, such as metal–organic frameworks.⁸³ Recently, a water-soluble and robust zirconium metal–organic framework was constructed by the coordination of zirconium chloride and an azobenzene-bearing π-aromatic ligand in organic solvent. Then, the payload rhodamine B could be tightly sealed by the noncovalent capping of pendant azobenzenes with β-CDs in water (Figure 8d).⁸⁴ Similar to the operating mode of the mechanized silica nanoparticles mentioned above, the loaded cargo could be released on command by UV irradiation or the addition of amantadine as a competitive guest without obvious premature leakage. Overall, the hierarchic organic–inorganic hybridization with photoresponsive CD-based components makes these integrated nanosystems potentially useful for the treatment of certain degenerative diseases, such as cancer.

Furthermore, the direct chemical modification of an azophenyl moiety onto the CD backbone offers an alternative and powerful strategy in the field of photosensitive supramolecular systems. It has been reported that azobenzene-bridged bis(permethyl-β-CD) can be conveniently synthesized by a click reaction, thus endowing this CD dimer with desirable photoresponsive capability.⁸⁵ The trans-isomer of a permethyl-β-CD dimer strongly bound amphiphilic tetraarylporphyrin to form an n,n polymeric assembly in aqueous solution, whereas the cis-form is prone to simply encapsulate the same guest molecule at a 1:1 binding stoichiometry. Consequently, after irradiation at 365 nm, the former gave hollow and curved tubular structures with large aspect ratios, but the latter exclusively formed solid nanoparticles. Interestingly, when the permethyl-β-CD units were replaced by the native ones, it was found that the photoisomerization of the azobenzene-bridged bis(β-CD) greatly altered the assembly morphologies and dimensions of adamantane-bearing diphenylalanine (Figure 9a).⁸⁶ The self-assembly of free dipeptides resulted in 1D nanofibers with a twisted β-sheet structure. Then, this fiber-like nanostructure instantly converted to 2D planar nanosheets in the presence trans-azobenzene-bridged bis(β-CD). Comparatively, the assembly between adamantyl diphenylalanine and cis-form azobenzene-bridged bis(β-CD) led to open-ended and curved...
tubular structures, and the interconversion between 1D nanotubes and 2D nanosheets could be efficiently regulated by light irradiation at 365 and 450 nm, respectively. The assembly mode in this photocontrolled morphological and dimensional conversion could be essentially attributed to the conformational differences in the host–guest complex upon the photoisomerization of the central azophenyl group. Thus, although one of the β-CD cavities was firmly occupied by the tumbled triazole moiety in water, the inclusion complexation of adamantyl diphenylalanine with the trans form of a host molecule adopted linear end-to-end conformation to further self-assemble as bilayer nanosheets, but a bent conformation became more dominant after the cis-isomerization of the host molecule and eventually led to the formation of tubular assemblies. Furthermore, it was also indicated that the 2D nanosheet exhibited a relatively higher dye absorption capacity and fluorescence enhancement than the 1D nanotubes toward Nile Red, likely due to the higher polarization of the cis isomer and the smaller
surface area of the nanotubular assembly. In spite of the limited dye loading ratio achieved, this work presents a successful example of performance-directed construction of biocompatible stimuli-responsive nanomaterials.

Despite the compelling photoisomeric features, common azobenzenes always suffer from some serious obstacles, which greatly impede their practical applications in clinic use. For example, the trans $\rightarrow$ cis isomerization triggered by harmful UV irradiation can induce unfavorable phototoxicity and low permeability, which may seriously impede the use of functional azobenzenes in biological tissues. Even worse, the spectral overlap of the trans and cis isomers can cause incomplete photoswitching and low phototransformation efficiency. Consequently, researchers have been devoted to the exploration of more biocompatible azo-compounds with tunable absorption wavelength and desirable adaptive capacity to CD hosts in the frontiers of photoresponsive supramolecular nanosystems.\[87\] Recently, Wu and co-workers reported a novel green-light-responsive azobenzene bearing four bulky isopropoxy groups at the ortho position, and, interestingly, the cis isomer could form a stronger inclusion complex with $\gamma$-CD than the trans isomer (Figure 8a, III).\[88\] These findings will definitely expedite the development of light-responsive host–guest nanosystems with the infrequently used $\gamma$-CDs.

Moreover, as a good supplement to the existing well-known azobenzene-based supramolecular systems, in 2016, Ravoo and coworkers developed a new type of heterocyclic azobenzene, namely, carboxylated arylazopyrazoles (AAPs, Figure 8a, II). The AAPs could achieve nearly quantitative photoisomerization at noninterfering excitation wavelengths, and the trans and cis isomers exhibited highly selective binding ability with $\beta$-CD.\[89\] Subsequently, the favorable photostationary states of AAPs have been successfully implemented in multivalent host–guest systems with CD-functionalized gold nanoparticles and CD-containing vesicles (Figure 9b). Moreover, the substituent effects and photophysical properties of AAPs have been comprehensively investigated by the same group, further confirming their excellent photoisomerization and biocompatibility.\[90\] In a recent study, taking advantage of the specific binding of PTX with the microtubular skeleton, Liu and co-workers successfully constructed a photocontrolled microtubule assembly mediated by the secondary inclusion complexation between PTX-modified $\beta$-CD and AAP (Figure 9c).\[91\] Benefiting from the high conversion efficiency of photochromic AAP, the photoresponsive aggregation and dispersion of microtubules could be reversibly phototuned upon alternating UV (365 nm) and visible-light (520 nm) irradiation, accompanied by a variety of morphological changes from nanofibers and nanoribbons to nanoparticulate assemblies with different sizes. More importantly, the supramolecular aggregation of microtubules could also be achieved in a cellular environment,

Figure 9. CD-based supramolecular assemblies with azo compounds: a) Nanosheet–nanotube interconversion by the supramolecular assembly between azobenzene-bridged bis($\beta$-CD) and adamantane-modified diphenylalanine.\[86\] b) Reversible aggregation and dispersion of i) $\beta$-CD-modified gold nanoparticles and II) amphipathic $\beta$-CD nanoparticles with trans- and cis-AAPs.\[89\] c-I) Photocontrolled aggregation of microtubules by PTX-modified $\beta$-CD and AAP. II) Colocalization of aggregated microtubules by the host–guest complex in A549 cells. 4',6-Diamidino-2-phenylindole dihydrochloride hydrate (DAPI), fluorescein isothiocyanate (FITC), and adamantane-bearing rhodamine B (RhB-ADA) were used to stain the nuclei, microtubules, and $\beta$-CD, respectively. Reproduced with permission.\[91\] Copyright 2018, Wiley-VCH.
resulting in pronounced cell shrinkage and relatively lower cell viability. This study provides the first demonstration that microtubule aggregation can be engineered at the molecular level by the synergetic combination with artificial stimuli-switchable components as functional building blocks.

5.2. Diarylethenes

As an intriguing class of photoactive molecules with unique physical and chemical properties, diarylethene and its analogues are known to have excellent photochromic activities, especially under UV and visible light irradiation (Figure 10a, I). Consequently, much effort has been devoted to the design and synthesis of diarylethene-based supramolecular systems by utilizing their photoswitchable isomerization between the ring-open and ring-closed states[92]. Although direct inclusion complexation with β- and γ-CDs can increase the photocyclization quantum yield of diarylethenes via enrichment of the antiparallel conformation in a constrained microenvironment,[93] the covalent modification of CD units onto the diarylethene
backbone is one commonly used method to fabricate CD–diarylethene nanoconjugates. One example of a method is a permethyl-β-CD dimer bridged by perhydrocyclopentene-based diarylethene, which can form nanofibrous structures with negatively charged porphyrin in water.[94] Furthermore, the energy transfer process from the included porphyrin to diarylethene core could be modulated by a photocyclization and cycloreversion reaction but with fairly low energy transfer efficiency and poor reversibility. These unsatisfactory results may arise from the following aspects: 1) the partial spectral overlap between the absorption spectrum of diarylethene and the fluorescence emission spectrum of porphyrin; 2) the low fatigue resistance of perhydrocyclopentene-based diarylethene that makes this host compound less light responsive; 3) the rigidified molecular structure of the host compound and the tightly compact supramolecular complexation that impedes the diarylethene core from efficient ring-closing and ring-opening cycles.

More gratifyingly, this situation is substantially improved in the case of a permethyl-β-CD dimer bridged by perfluorocyclopentene-based diarylethene. Owing to the more π-conjugated molecular structure and the electron-withdrawing property of the perfluorocyclopentene counterpart, the UV–vis absorption of this optimized host compound can bathochromically shift into the long-wavelength region, thus leading to the perfect spectral matching between the porphyrin donor and the diarylethene acceptor.[95] By comparing the fluorescence emission intensity of porphyrin before and after photocyclization of diarylethene, the Förster resonance energy transfer efficiency in this binary nanosystem was calculated to be above 90%, and the fluorescence emission of porphyrin could be reversibly regulated by the photochromism of diarylethene without an obvious light-fatigue phenomenon. Importantly, the fraction of singlet oxygen (1^2O_2) produced by the photosensitized porphyrins could be further reversibly photocontrolled in water due to the close correlation between the fluorescence emission of optical agents and the generation of reactive oxygen species via intersystem crossing from singlet to triplet excited states. It is believed that such a biocompatible photoswitchable nanosystem can be developed as a promising nanoplatform for selective fluorescence visualization and photodynamic therapy arising from the efficient and reversible fluorescence emission and 1^2O_2 generation. Based on this strategy, a ternary nanoparticulate assembly has been constructed by incorporating dithienylethene-bridged bis(permethyl-β-CD) and amphiphilic porphyrin with cyanine dye as the essential component (Figure 10a, II).[96] When the dithienylethene core was subjected to its ring-closed state under UV irradiation, the intermolecular energy transfer process from the porphyrin to the cyanine dye was immediately terminated, and no fluorescence was observed (Figure 10a, III and IV). Superior to the previously mentioned binary nanosystem,[95] the introduction of a hydrophobic cyanine dye facilitated an effective energy transfer from the included porphyrin to the embedded cyanine fluorochrome, thereby leading to a dramatic enhancement of fluorescence intensity at ~700 nm. Therefore, this light-triggered ternary nanoparticulate assembly provides a good perspective on the facile construction of stimuli-responsive photoluminescent materials for biosensing and fluorescent probes.

### 5.3. Other Types of CD-Based Photoresponsive Nanossemblies

A variety of photochemical reactions, such as photo-crosslinking, photodimerization, and photocleavage, have been extensively employed in CD-based biofunctional nanosystems.[97] For example, pyrenylmethyl and o-nitrobenzyl esters were used as photocleavable linkers in the construction of CD-based supramolecular vesicles and nanowaves, thus leading to light-induced disaggregation[98] and cargo release.[99] Respectively. In another case, an unnatural phenylalanine mutated antibody was site-specifically photocoupled to the β-CD-immobilized surface via UV irradiation for use in affinity proteomics.[100] Thiol–allylether photopolymerized hydrogels with tunable stiffness were also constructed by inclusion complexation between the chemically immobilized β-CD and four-arm PEgylated adamantane and could be used in the regulation of cell fate processes.[101] In addition, the complexation-induced photodimerization of coumarin-modified diphenylalanine in the cavity of γ-CD could induce a morphological conversion from 1D nanofibers to 2D thin films, and the latter nanostructure could be further utilized in the clearance of pollutants from water through filtration.[102]

Furthermore, the combined advantages of pH- and photo-responsiveness have given rise to controlled supramolecular nanosystems using photoacids, which are molecules that can reversibly undergo proton association and dissociation upon light irradiation at different wavelengths (Figure 10b, I).[103] Taking advantage of these structural features, different research groups have provided impressive examples of tunable supramolecular nanosystems that utilize the photoacid-triggered protonation–deprotonation process.[104] For instance, based on their previous work on metal coordination-mediated linear polyseродorotoxanes,[105] Liu and coworkers recently developed a light-controlled nanorod-like superstructure constructed via coordination of Zn^2+ with a 4,4′-dipyridine-β-CD inclusion complex (Figure 10b, II).[106] Interestingly, the association and disassociation of such nanorod assemblies could be reversibly regulated by alternating light irradiation of the photocyclable merocyanine in aqueous media. Moreover, for cargo release applications, Zink and co-workers reported an α-CD-capped mesoporous silica nanoparticle with an attached pyrene-based photoacid, and fluorescent molecules entrapped in the nanoparticles could be continuously released when the aniline-containing stalk was acidified by photoacid-driven proton transfer.[107]

To date, many photoactivated combinational therapies have been successfully implemented using CD-based supramolecular nanosystems for wider biomedical applications.[108] In one case, a reduction-sensitive multicomponent polymeric prodrug was developed by the inclusion complexation of HACD with a disulfide-linked adamantane derivative bearing CPT as the anticancer drug and naphthalimide as the fluorescent probe (Figure 10c).[109] Then, the near-infrared absorbing dye IR825 was embedded into the nanoparticulate assembly, further allowing a light to heat conversion for photothermal therapy. As a result, in vitro fluorescence visualization and in vivo synergistic chemotherapeutics for tumors could be achieved after the embedded disulfide bonds were efficiently cleaved under the reducing environment in cancer cells. In another case, a
core–shell–shell upconversion nanoparticle was constructed and equipped with methylene blue as the photosensitizer and rhodamine B as the model drug (Figure 10d).\[110\] When irradiated at 980 nm, green 540 nm light was emitted for cell imaging, and the red 660 nm light was employed for singlet oxygen generation. The singlet oxygen arising from the photosensitizer activation could be further used in thermodynamic therapy and in dissociation of β-CD capping agents for the release of model molecules.

6. Magnetoresponsive CD-Based Supramolecular Assemblies

In addition to the aforementioned light-responsive biomaterials, materials responsive to a magnetic field also hold prominent positions because they have critical relevance to natural phenomena and physiological events.\[111\] For instance, some insects and magnetotactic bacteria use the geomagnetic field to orient and navigate along their migratory paths. Previously, studies on CD-based magnetism-responsive supramolecular assemblies primarily focused on metallic oxide magnetic cores encrusted with CD moieties that could be applied in water purification\[112\] and the separation of organic/inorganic micropollutants.\[113\] However, presently, with the unprecedented progress in bioinspired stimuli-responsive nanomaterials, the potential applications and popularity of magnetoresponsive supramolecular assemblies have dramatically increased in recent years.\[114\] Magnetic nanoparticles have been extensively exploited as magnetic resonance imaging agents, drug/gene delivery nanocarriers, and therapeutic nanoplatforms with high biosafety and biocompatibility for many biomedical applications.\[115\]

![Figure 11. CD-based magnetoresponsive supramolecular assemblies: I) Formation of binary supramolecular nanofibers via cross-linking of HACD with mitochondrion-targeting peptide-modified magnetic nanoparticles (MitP-MNP). II) Confocal microscopy images of the growth of MitP-MNP⊂HACD nanofibers along the direction of the geomagnetic field. III) Schematic illustration of tumor cell invasion in a Matrigel invasion model, showing an enhanced inhibition effect induced by MitP-MNP⊂HACD nanofibers. IV) In vivo inhibition of A549 cell metastasis by MitP-MNP⊂HACD nanofibers. All panels reproduced with permission.\[119\] Copyright 2018, American Association for the Advancement of Science.]

Remarkingly, the heat generated from magnetic spin relaxation in many magnetothermally responsive nanoparticles can be further developed for magnetothermal cancer ablation treatment.\[116\] In line with these tremendous potential applications, it is anticipated that the synergistic integration of CDs and magnetic particles into a single supramolecular entity will facilitate the creation of more innovative biomaterials and pave a new avenue for smart precision medicine.\[117\] For example, targeted imaging and precise therapy have been achieved by theranostic β-CD-modified magnetic mesoporous silica nanoparticles.\[118\] The significant inhibition of cancer growth mediated by these nanoparticles was jointly attributed to selective receptor-mediated internalization, specific prodrug release, high contrast in magnetic resonance imaging, and magnetically enhanced permeability and retention effect at tumor sites.

Nevertheless, compared with the strong artificial magnetic field, magnetism-responsive nanosystems that can precisely respond to the very weak magnetic field of the earth have only sporadically been reported. Moreover, compared with early-stage cancers and primary tumors present before the development of a cancerous mass, distant invasion and metastasis are the main obstacles hampering the clinical translation of stimuli-responsive biomaterials in cancer treatment. With these issues in mind, Liu and coworkers recently constructed a magnetic and photo dual-controlled nanoassembly for the suppression of tumor invasion and metastasis (Figure 11, I).\[119\] After being decorated with a mitochondrion-targeting peptide, the inorganic magnetic nanoparticles could form well-defined fibrous nanostructures via multiple noncovalent binding with an HACD polymer. In the inanimate milieu, these obtained nanofibers not only showed light-sensitive assembly and disassembly behaviors induced by photochromic AAP but also...
presented directional aggregation under both an artificial and the earth’s magnetic field (Figure 11, II). At the subcellular level, the supramolecular nanofibers recruited isolated mitochondria growing along the direction of (geo)magnetic fields in a controlled manner. In the intracellular environment, the supramolecular nanofibers specifically localized at the mitochondria region, thus leading to severe mitochondria damage and decreased cell viability. Furthermore, the intercellular formation of binary supramolecular nanofibers severely attenuated cell invasion into Matrigel (Figure 11, III). In an animal model, tumor-bearing mice treated with the supramolecular nanofibers showed a high survival rate due to the geomagnetic field-activated inhibition of the metastatic spread of tumor cells (Figure 11, IV). This work proposed a new operating model for cancer therapy and to be envisaged, such intelligent biomaterials triggered by the intrinsic geomagnetic field can easily be adapted for treatment of other invasive and degradative diseases.

7. Summary and Outlook

In this review, we summarized the research progress made, primarily in the past three years, in developing CD-based stimuli-responsive supramolecular assemblies and introduced their related biological functions by selecting some representative examples. The potential biological applications of these supramolecular materials have been widely extended from biological sensing, drug delivery and release, and the regulation of intra-/intercellular communication to disease diagnosis and treatment. In particular, many biofunctional moieties, such as folic acid, biotin, and hyaluronic acid, have been covalently modified onto the CD’s backbone to endow them with desirable cell/tissue-targeting abilities. Despite the remarkable advances in the field, a great deal of effort is required to master the structure–activity relationships and promote their practical applications. The development of conceptual and theoretical guidance is a prerequisite condition since it not only aids in the exploration of new stimuli-responsive counterparts with the capacity to be adapted for use with CDs but also facilitates performance-targeted design and construction. From a personal perspective, the following aspects may deserve our careful attention.

i) With the exception of the mono- and per-substituted β-CDs at the primary face, there are still tremendous challenges in expanding the use of other types of CDs, and the number of methods for the regioselective modification of CD’s skeleton is fairly limited. Thus, it is imperative to establish more efficient synthetic strategies that will enrich the field of CD-based multistimuli-responsive nanosystems. Alternatively, the site-selective poly-hetero-functionalization of CDs is now possible, which will definitely provide more advanced applications in diverse areas.

ii) Moreover, currently, solubilization and transportation by monovalent CD-drug associations does not meet the high criteria for personalized, precision medicine. Therefore, orthogonal and multivalent interactions are always necessary to enhance binding affinity in the CD-based molecular recognition process as recently exemplified by the multivalent host-guest binding between polymer-CD and polymer-PTX to achieve more effective anticancer therapy in a mouse tumor model. In addition, highly controlled molecular recognition involving modified CDs has not been well established for biomedical applications; for example, the commonly used adamanate and azobenzene guest molecules do not have sufficient biological implications and functions.

iii) The biological functions of CD-based supramolecular assemblies are mainly confined to their anticancer activities, and there is a relative paucity of studies on the treatment of other acute and chronic diseases worldwide, such as cardio- and cerebrovascular diseases. For instance, cholesterol accumulation is a hallmark of atherosclerosis, and the strong complexation of cholesterol with functionalized CDs has been favorably exploited for atherosclerosis regression. To this end, CD-based enzyme-responsive nanoassemblies may provide new possibilities in this field because the up- and down-regulation of enzymatic activity are involved in a number of severe pathological processes.

iv) Some of the currently available supramolecular nanostructures are overengineered and wasteful both in materials and cost. These nanostructures always require tedious chemical synthesis and time-consuming purification, which entirely negates the innate superiority of noncovalent interactions in supramolecular chemistry. Even worse, the complex molecular design of overengineered nanosystems can further decrease the cargo-to-carrier mass ratio. In addition, although CD derivatives are believed to be essentially nontoxic, the biosafety of the nanocarriers themselves has not been adequately addressed. Thus, there is an urgent need to simplify and optimize the chemical composition of CD-based biofunctional nanoarchitectures.

v) Finally, in most cases, the chemical redox and pH variance usually engender chemical waste in the system. To alleviate this problem, remote and noncontact control over the chemical and biological performance by advanced physical stimuli become inevitable necessities for fabricating next-generation supramolecular biomaterials. In this regard, field-responsive nanomaterials that are sensitive to light irradiation, high-frequency ultrasound, or an oscillating magnetic or electric field have recently stimulated an upsurge of research interest. Through the innovative combination of these unconventional triggers, we envisage that more CD-based nanoassemblies will eventually be successfully translated into therapeutics for patients.

In conclusion, in the past few decades, we have witnessed substantial development in CD-based nanosystems from a single inclusion complex to multicomponent assembly; from single- to multistimuli-driven molecular aggregation; and from single- to multimodal theranostics against many devastating diseases. CD-based supramolecular assemblies with pH-, redox-, enzyme-, photo-, and magnetism-sensitivities can be functionalized into versatile nanoplates capable of accomplishing multiple tasks under physiological conditions. The selection of chemical, biological, and physical stimuli and their controlled operational modes described in this review can also be applicable to different types of macrocylic receptors, such as cucurbiturils and pillararenes. Indeed, more new discoveries
can be stimulated to further promote the practical development of CD-based stimuli-responsive nanosystems, which may allow us to fully understand the dynamic nature of biological events and bring about a positive and substantial influence on human health.

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Conflict of Interest

The authors declare no conflict of interest.

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