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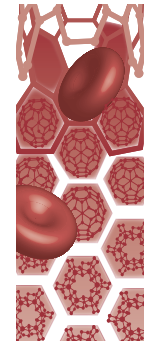

Nanoparticles functionalized with supramolecular host–guest systems for nanomedicine and healthcare

Synthetic macrocyclic host compounds can interact with suitable guest molecules via noncovalent interactions to form functional supramolecular systems. With the synergistic integration of the response of molecules and the unique properties at the nanoscale, nanoparticles functionalized with the host–guest supramolecular systems have shown great potentials for a broad range of applications in the fields of nanoscience and nanotechnology. In this review article, we focus on the applications of the nanoparticles functionalized with supramolecular host–guest systems in nanomedicine and healthcare, including therapeutic delivery, imaging, sensing and removal of harmful substances. A large number of examples are included to elucidate the working mechanisms, advantages, limitations and future developments of the nanoparticle–supramolecule systems in these applications.

Keywords: healthcare • nanomedicine • nanoparticles • pollutant removals • sensing • supramolecular host–guest system • therapeutic delivery

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In recent decades, molecular sensing, therapeutic delivery and removal of harmful substances have been at the core of nanomedicine and healthcare. For example, the increasing amount of industrial pollutants in the environment puts human health under serious threat, which raises the need for harmful substance detection and subsequent removal. The effective disease prevention and therapy requires fast, accurate and convenient methods for disease diagnosis and therapeutic delivery. The rapid development of nanotechnology has provided new solutions to these emerging problems by enabling the novel nanomaterials and nanosystems with superior imaging, sensing, delivery and removal functions at the molecular level [1–7].

In particular, nanoparticles and supramolecular host–guest systems have attracted strong interests for applications in nanomedicine and healthcare. The supramolecular systems employ the noncovalent interactions between guest molecules and host compounds for various biomedical functions such as capture and spatial localization of analytes, and drug and gene encapsulation [8–12]. So far, plenty of macrocyclic host molecules, including crown ethers [13], calixarenes [14], cucurbit[n]urils (CB[n]) [15], cyclodextrins (CDs) [16], cyclophanes [17] and pillarenes (or pillar[n]arenes) [18], have been applied to constitute such supramolecular systems.

Gold and silver nanoparticles exhibit remarkable optical and chemical properties [19–24]. Together with their facile synthesis, biocompatibility and ease of functionalization, these noble metal nanoparticles have already been used in disease diagnosis and therapy [25–28]. Magnetic nanoparticles (MNPs) have been utilized for tissue repair, immunoassays, MRI and cell manipulation because of their biocompatibility, superparamagnetism and small sizes [29–34]. Mesoporous silica nanoparticles (MSNs) have generated interests as therapeutic delivery vehicles [35]. Numerous pore channels penetrating through the particles with pore openings on the surfaces of MSNs enable the storage of large amount of drug molecules within the MSNs as well as the controlled release of

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the drug at designated locations in response to external stimuli [36–38].

Among the developments of the more sophisticated nanosystems for the better applications in nanomedicine and healthcare, the marriage of supramolecular host–guest structures and nanoparticles shows great promises for enhanced or novel applications [39–41]. For example, the macrocyclic host molecules on nanoparticles help enhance multiple biomedical functions, such as the permeability of nanoparticles into target tissues [42], the recognition of analyte molecules [43], and the load of drug molecules on the surfaces [44] or within the pores of nanoparticles [37]. On the other hand, the nanoparticles offer the largely enhanced drug loading capacity and the real-time monitoring of therapeutic delivery and therapeutic effectiveness. So far, tremendous progress has been made in the design and applications of nanoparticles functionalized with supramoleclar host–guest systems in nanomedicine and healthcare. In this review, we focus on three major applications, in other words, therapeutic delivery, sensing and removal of harmful substances. The therapeutic delivery applications are further divided into two sections, in other words, nanogatekeepers (section 'Supramolecular host–guest systems as nanogatekeepers on mesoporous nanoparticles for therapeutic delivery') and nanocontainers (section 'Supramolecular host–guest systems as nanocontainers on nonporous nanoparticles in therapeutic delivery'), according to the different roles of supramolecular host–guest structures in the integrated nanosystems. The section 'Nanoparticles functionalized with supramolecular host–guest systems for sensing applications' and the section 'Nanoparticles functionalized with supramolecular host–guest systems for removal of harmful substances' cover the sensing and the removal of harmful substances, respectively. We conclude this review with an executive summary and future perspective.

Supramolecular host–guest systems as nanogatekeepers on mesoporous nanoparticles for therapeutic delivery

One of the most promising integrations of nanoparticles and host–guest systems for nanomedicine is the mechanized MSNs for therapeutic delivery. In such integrated nanosystems, a MSN serves as a drug container holding drug molecules in its pores and the supramolecular host–guest system serves as the nanogatekeeper on the openings of the pores for controlled drug release. Since the proof-of-principle study for the host–guest systems as nanogatekeepers on MSNs [45], hundreds of studies have been done to investigate a variety of such integrated nanosystems for smart therapeutic delivery. Supramolecular host–guest nanogatekeepers on MSNs can be fitted into three types, in other words, nanovalves, nanopistons and snap-top nanomachines, according to their structures and functions.

A supramolecular nanovalve consists of a macrocyclic host molecule circling a guest molecule as a stalk immobilized on an MSN (Figure 1). The host molecule, which is noncovalently bonded with the stalk, can slide along the stalk in response to external stimuli to block and unblock the pore openings on the MSN. For the nanopiston, the cyclic host molecule is tethered to the surface of an MSN and the guest molecule as a stalk is held in the cyclic cavity through the guest–host interactions. During the drug release process, the guest molecule moves out of the host cavity in response to external stimuli, which leaves the cavity of the host molecule unblocked and allows the release of cargo molecules that are smaller than the cavity. The larger cargo molecules can only be released by dethreading the cyclic host molecules from the surfaces of MSNs. A snap-top nanomachine, which also consists of a macrocyclic host molecule encircling a guest molecule immobilized on a MSN, includes a stopper group at the distal end of the guest molecule that holds the host molecule. The opening of the pore is achieved by dethreading the host molecule from the guest molecule through the stimulus-induced 'snap' of the stopper group. So far, a variety of mechanized MSNs using the three types of supramolecular host–guest systems have been demonstrated. Herein, we structure them into ten categories based on activation methods that trigger the mechanical motions in supramolecules and thus the controlled release of drug molecules from the MSNs (Figure 1).

Activation through redox

The seminal work on nanovalve-based therapeutic delivery systems involves host–guest systems activated by redox chemistry [45]. Figure 1A illustrates a representative redox supramolecular host–guest systems on the MSNs, in which ferrocenecarboxylic acid stalks and β-CDs serve as guest and host molecules, respectively [46]. To release the cargo molecules, in other words, rhodamine B, from the pores of MSNs, a voltage of 1 V was applied to cause the electrochemical oxidation of the ferrocence units and the resultant dissociation of the host–guest systems. This work has paved the way toward redox-active release of drugs for cancer treatment [47].

Activation by UV light

Light activation has several advantages: light has high switching speed, work without producing chemical waste, and can be used for dual purposes – controlling and monitoring therapeutic delivery [48]. Most of the

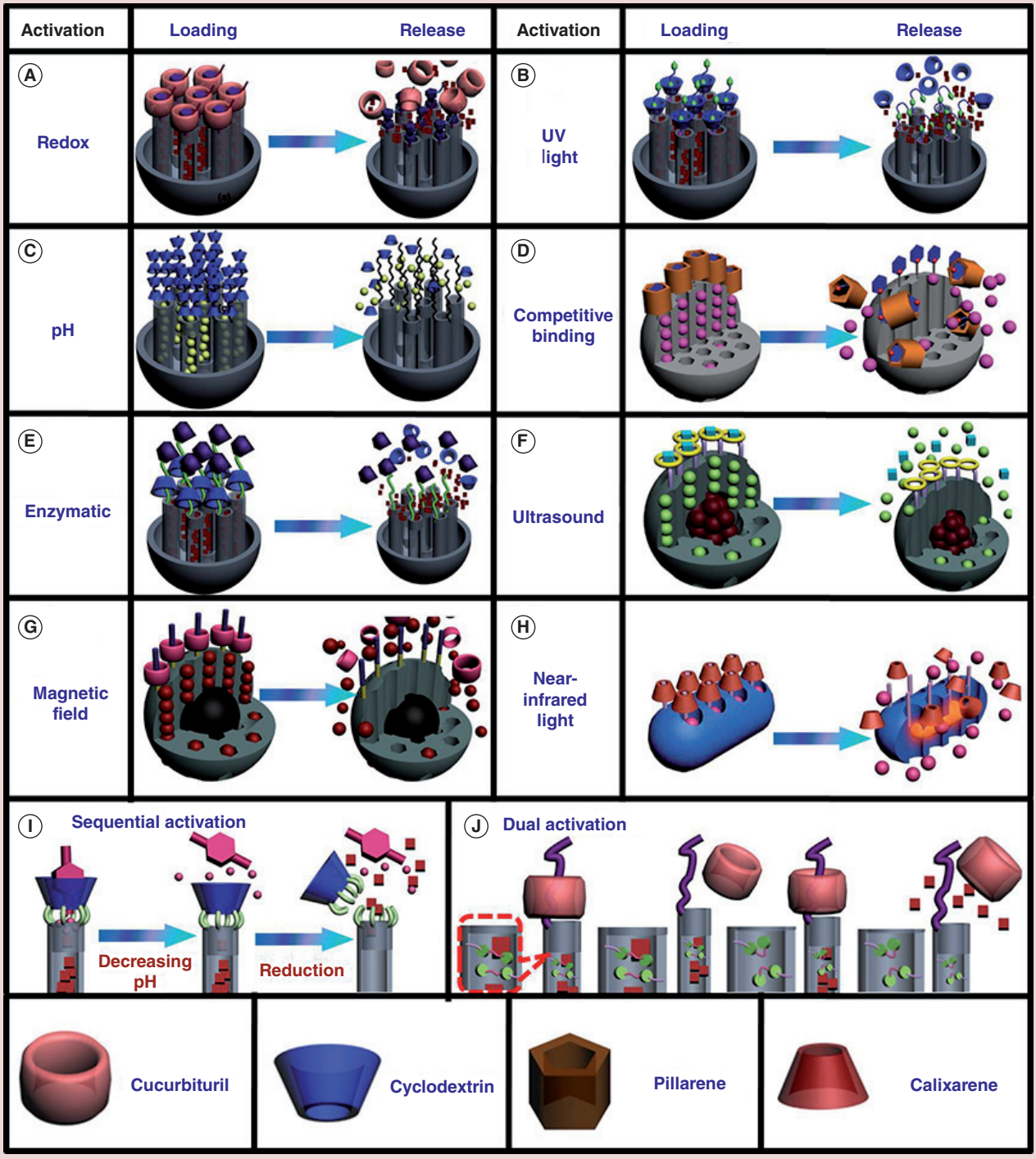

Figure 1. Schematic illustration of ten types of nanogatekeepers based on supramolecular host–guest systems according to activation methods. **(A)** Redox activation; **(B)** UV-light activation; **(C)** pH activation; **(D)** competitive binding activation; **(E)** enzymatic activation; **(F)** ultrasound activation; **(G)** magnetic field activation; **(H)** near-infrared light activation; **(I)** sequential activation; and **(J)** dual activation.
For color figures, please see online at www.futuremedicine.com/doi/full/10.2217/NNM.15.1

light-activated mechanized MSNs have relied on UV-switchable guest molecules. Figure 1B illustrates a representative nanosystem based on the *trans-cis* photoisomerization of azobenzene (AB) molecules on MSNs [49]. In this example, MSNs were functionalized with AB-containing stalks, (E)-4-([4-(benzylcarbamoyl)phenyl]

diazenyl)benzoic acid. Initially, AB was at the *trans* state and β-CDs circled the (E)-4-([4-(benzylcarbamoyl] phenyl)diazenyl)benzoic acid, sealing the pores of the MSNs. Upon irradiation with a 351 nm laser beam, AB isomerized from *trans* to *cis* configuration, leading to the dissociation of β-CDs from AB stalks and the release of cargo molecules because the binding affinity between β-CDs and *trans*-AB derivatives is higher than that between β-CDs and *cis*-AB derivatives [50,51]. With the design of AB molecules that are switchable at visible wavelength, this activation mechanism was used for *in vivo* therapeutic delivery to optically transparent zebra fish larvae [52]. Pulsatile therapeutic delivery for effective therapy of certain diseases has also been achieved based on pulsed light irradiation [53].

Recently, polymers have also been applied in the light-activated host–guest systems for therapeutic delivery to achieve robustness and high on/off ratio of drug release. One example is the use of CDs grafted onto star-shaped poly(glycidyl methacrylate) [54]. The CD-appended polymers were employed to cover the surface of MSNs as nanogatekeepers. Irradiation of UV light opened the nanogatekeepers and allowed the cargo molecules to diffuse out of the pores. These polymer-based nanogatekeepers are not restricted by the pore sizes of MSNs, enabling the controlled delivery of various drug molecules, nucleic acids and peptides.

Activation by change in pH

pH activation of therapeutic delivery has significant impacts on diseases that cause local changes in pH value. For instance, cancerous cells can thrive in the more acidic environments than healthy cells. Several pH-activated supramolecular host–guest systems on MSNs have been demonstrated [55,56]. For example, Kim *et al.* developed a pH-activated therapeutic delivery system based on the pH-responsive snap-top nanomachines on MSNs [57]. As shown in Figure 1C, polypseudorotaxanes that are consisted of polyethylene-imine and CDs work as nanogatekeepers. The CDs began to dethread from the polyethylene-imine when the pH value is lower than 8, releasing the drug molecules [58,59].

Activation by competitive binding

In competitive binding activation, guest molecules can be dethreaded from the host molecules to release drug molecules by adding the third molecules that have the stronger affinity to the host molecules. This type of activation offers a new strategy for the potential treatment of diseases such as Parkinson's disease where the high concentration of competitive binding agent, acetylcholine, near the synapse sites in a Parkinson's disease patient's body can be used to trigger the release of drug molecules. Figure 1D illustrates one example, which is based on carboxylatopillar[5]arenes (CP[5]As) in pyridinium stalks immobilized on MSNs [60]. The presence of competitive binding agents, methyl viologens (MVs), which have the higher binding affinity ($K_a \approx 8 \times 10^4\ M^{-1}$) to stalks than CP[5]As ($K_a \approx 2.5 \times 10^3\ M^{-1}$), makes CP[5]As dethread from the stalks and releases the drug molecules [61]. The drug release profiles and kinetics based on competitive binding activation can be adjusted by controlling the concentration of triggering molecules [62].

Enzymatic activation

Enzymatic activation features high accuracy, specificity, efficiency and biocompatibility. Zink *et al.* reported mechanized MSNs that were activated by enzyme known as porcine liver esterase [63]. As illustrated in Figure 1E, tri(ethylene glycol) and α-CD served as guest and host molecules, respectively. The α-CD can be dethreaded from the tri(ethylene glycol) upon the porcine liver esterase catalyzing hydrolysis. A series of experiments have shown that the ester-stoppered snap-top nanomachine is efficient in the enzyme-activated release of drug molecules. In another example, two types of stalks with different enzyme cleavable sites were employed to form the nanogatekeepers with macrocyclic host molecule known as sulfonatocalix[4]arene [64]. It has been shown that esterase and urease can selectively activate the ester-linked and urea-linked tethers.

Activation by applied ultrasound

Ultrasound is a popular energy source for medical imaging and therapeutics [65,66]. Leung *et al.* have demonstrated ultrasound activation of mechanized MSNs [67]. As illustrated in Figure 1F, the MSN is a superparamagnetic iron oxide/mesoporous silica core/shell nanoparticle. Dibenzo-crown ethers were immobilized onto the pore entries of the shell. These crown ethers encapsulated different metal ions (Na^+ or Cs^+) as capping agents to form host–guest systems as nanogatekeepers. Upon the application of ultrasound, Na^+ captions were dissolved into solution and the cavities of crown ethers were loaded with H^+. The newly formed crown ether-H^+ complexes could no longer block the pores on the mesoporous silica and the drug molecules were released. The effectiveness of ultrasound actication depends on relative strength between the agent–crown interactions and the ultrasound intensity. The ultrasound activation has paved the way toward remote, noninvasive therapeutic delivery guided by ultrasound imaging.

Activation by applied magnetic field

Magnetic field activation represents another remote, noninvasive therapeutic delivery. Zink *et al.* developed

zinc-doped iron oxide nanocrystals/mesoporous silica core/shell nanoparticles functionalized with supramolecular host–guest systems for therapeutic delivery with magnetic field activation of [68]. As illustrated in Figure 1G, the nanogatekeepers consisted of cucurbit[6]urils (CB[6]s) as host molecules and tetraethyl orthosilicates as guest molecules. Upon the application of an oscillating magnetic field, zinc-doped iron oxide nanocrystals generated local heating due to the hyperthermic effects. The temperature increases led to the opening of the nanogatekeepers, and in effect, the diffusion of drug molecules from the pores. The results also indicated that additional pulses continued to release the cargo molecules.

Activation by applied near-infrared light

UV and visible light suffers from the low penetration in tissues. In addition, over exposure to UV light is harmful to human body. In contrast, near-infrared (NIR) light is a better option for biomedical applications due to its low loss in tissues and safety. Recently, gold nanorod/mesoporous silica core/shell nanoparticles have been developed for the NIR activation [69]. As illustrated in Figure 1H, the nanogatekeepers consisted of quaternary ammonium salt stalks encircled by sulfonatocalix[4]arene guest molecules. Au nanorods absorbed and converted NIR light into local heat via the excitation of localized surface plasmon resonances (LSPRs), which reduced the binding affinity between the sulfonatocalix[4]arene and quaternary ammonium salt and thus dissociated the nanogatekeepers for the release of drug molecules. The release profile and kinetics of this nanosystem was controllable with the laser power. The NIR activation has significantly increased the tissue penetration for effective *in-vivo* applications.

Sequential activation

The better therapeutic effects are achieved for some complicated diseases with sequential release of different types of drugs [70,71]. Recently, dual-cargo release has been demonstrated using MSNs functionalized with nanopistons consisted of β-CD rings and methyl orange (MO) plugs [72]. Two types of cargo molecules (Hoechst 33342 and CA) with different sizes (approximately 20 Å and 4.5 Å, respectively) were loaded into the pores of MSNs in sequence. As illustrated in Figure 1I, the β-CD rings that were bonded with the outer rims of the pores through disulfide units served as nanogatekeepers for Hoechst 33342. The MO plugs that were encapsulated by the β-CD rings served as nanogatekeepers for CA. The decrease of pH value of the solution expelled the protonated MO plugs from the cavities of β-CDs, causing the CA molecules to diffuse through the β-CD rings into the solution. Adding 2-mercaptoethanol as a reductant to cleave the disulfide bonds achieved subsequent release of Hoechst 33342.

Dual activation

The more sophisticated control of drug release is achieved with activation based on logic processes of two or more external stimuli [73]. For example, nanoimpellers and nanovalves were utilized simultaneously for dual activation of drug release. As illustrated in Figure 1J, photoresponsive AB derivative was tethered to the inner pore wall of the MSNs to serve as nanoimpeller, and the supramolecular host–guest system consisted of a CB[6] ring and a bisammonium stalk was immobilized on the outer rim of the pores to serve as the nanovalve. When the incident light is absorbed by both the *trans* and *cis* configurations, the continuous irradiation of light can lead to a dynamic wagging motion of AB to expel the cargo molecules out of the pores. Meanwhile, the closing and opening of the nanovalves can be controlled by pH value. The combination of nanoimpellers and nanovalves enables an AND logic type of therapeutic delivery nanosystems in which the cargo molecules can only be released from the pores by simultaneously applying light irradiation that activates the nanoimpellers and adding NaOH that opens the nanovalves.

In summary, MSNs functionalized with supramolecular host–guest systems provide the versatile approaches toward the controlled release of drugs and biomolecules for therapeutic purposes. With the rational design and tailored synthesis, supramolecular host–guest systems that are responsive to various stimuli have been demonstrated for the targeted applications. Some of activation methods such as redox [47], pH [68,74], have been applied for the *in vivo* delivery of drugs into living cells, including breast cancer cells, myeloid cells and Hela cells. With the proper surface functionalization of nanoparticles, targeted therapeutic delivery into tumor cells has been achieved [47,75]. Despite the tremendous progress, two major challenges have to be solved before the MSNs functionalized with the supramolecular host–guest systems are translated into the clinical applications. One is to systematically compare the delivery efficiency and accuracy of different systems to facilitate the identification of the best option for a given application [76]. The other is to improve the understanding of the biosafety of the nanoparticle–supramolecule systems. Although the biocompatibility of MSNs has already been studied for their *in vivo* applications [75], supramolecules on the nanoparticles can cause changes in the physiochemical properties of the hybrid nanosystems and the biological responses, requiring the systematic research

on the biosafety of the nanosystems under the clinical environments.

Supramolecular host–guest systems as nanocontainers on nonporous nanoparticles in therapeutic delivery

Rather than the employment of porous structures for the holding of therapeutic materials, nonporous nanoparticles, when interfaced with supramolecular host–guest systems that work as nanocontainers, can also carry therapeutic molecules for on-demand release at the target cells and tissues. Drug molecules are trapped either inside the host molecules [77] or around the host–guest systems [78]. The nanocontainer functions enable acute release and reduce the side effects of the drug molecules on healthy cells [79,80]. Without the requirement on porosity, one can significantly expand the types of nanoparticles that can be used in nanomedicine. Furthermore, the nanoparticles in the integrated nanosystems can function as delivery vehicles and/or imaging agents. Herein, we structure the nanocontainer applications of supramolecular host–guest systems on nanoparticles into three categories, in other words, drug molecules as guests, drug sequestration and protein immobilization, as discussed in the following sub-sections.

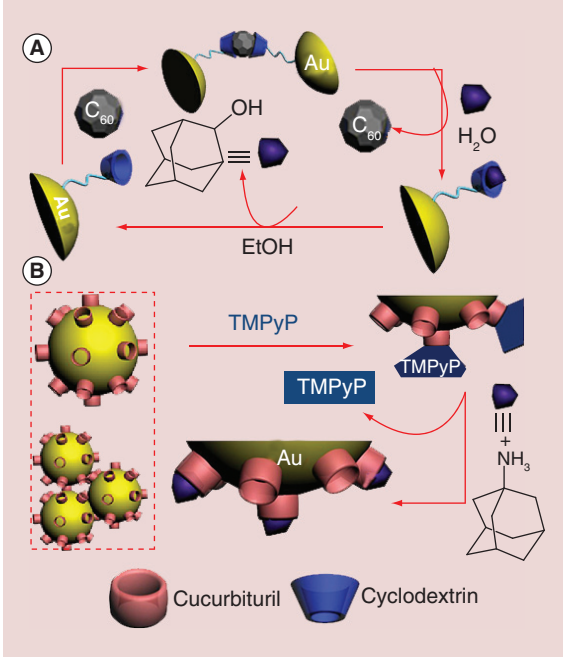

Figure 2. Schematic illustrations of supramolecular host–guest systems as nanocontainers. (A) Schematic of gold nanoparticles functionalized with Tβ-CD as recycling extractor of C_{60}. The captured C_{60} can be released by adding 2-adamantanols; **(B)** schematic of the recognition and release mechanism for TMPyP by silver nanoparticle conjugates functionalized with CB[7]s. The TMPyP can be released from the CB[7]s by adding 1-amantadine hydrochloride.
C_{60}: [60]fullerene; TMPyP: 5,10,15,20-tetrakis(4-N-methylpyridyl) porphyrin.

Drug molecules as guests

One of the most common strategies for containing drugs in supramolecular host–guest systems is the encapsulation of drug molecules into the host units. In their initial study, Liu *et al.* produced Tβ-CD-modified Au nanoparticles that captured and released C_{60} [81]. As shown in Figure 2A, the CD hosts selectively captured C_{60} to form host–guest systems, and the C_{60} was released by adding 2-adamantanols to substitute C_{60} as guest molecules due to the higher binding ability between 2-adamantanol and the CD cavity [82]. Mohanty *et al.* used CB[7]-functionalized Ag nanoparticles to capture the porphyrin derivatives, including TMPyP, which have potential applications in photodynamic therapy [44]. The drug molecules were encapsulated as guest molecules inside the CB[7]s by the host–guest interaction and were released by adding 1-amantadine hydrochloride (Figure 2B).

A route-controllable carrier is needed for the intracellular therapeutic delivery in order to reduce the side effects [83,84]. MNPs are considered as such a promising therapeutic delivery carrier due to their controllability with a magnetic field, tunable particles sizes and shapes and good biocompatibility [85,86]. Cai *et al.* designed β-CD-functionalized MNPs that contained drug molecules (known as diazepams) in the host cavities of β-CDs [87]. The drug-loaded nanoparticles were routed with an external magnetic field. Later on, an integrated nanosystem consisted of MNPs and β-CD grafting polyethylenimine has been developed to further improve the cellular uptake efficiency [79]. The cancer drug (known as camptothecin) encapsulated into the cavity of β-CD was controllable with both redox agents and external magnetic fields.

Recently, the multi-functional applications centered on the nanocontainers have been demonstrated using nanoparticles functionalized with supramolecular host–guest systems. Trabolsi *et al.* developed a dual-functional system based on CB[7]-functionalized MNPs, which enables both therapeutic delivery and *in vivo* imaging [29]. Poly-therapeutics has also been demonstrated, which enables the simultaneous delivery of multiple medical agents to targeted cells and tissues for enhanced treatments [88,89]. As illustrated in Figure 3, Mao *et al.* developed β-CD-functionalized quantum dots (QDs), which encapsulated doxorubicin (DOX) and siRNA for both cancer chemotherapy and chemo-gene therapy [90]. The siRNA significantly reduces the level of drug resistance gene expression in Hela/DOX cells and, as a result, the intracellular accumulation of DOX and

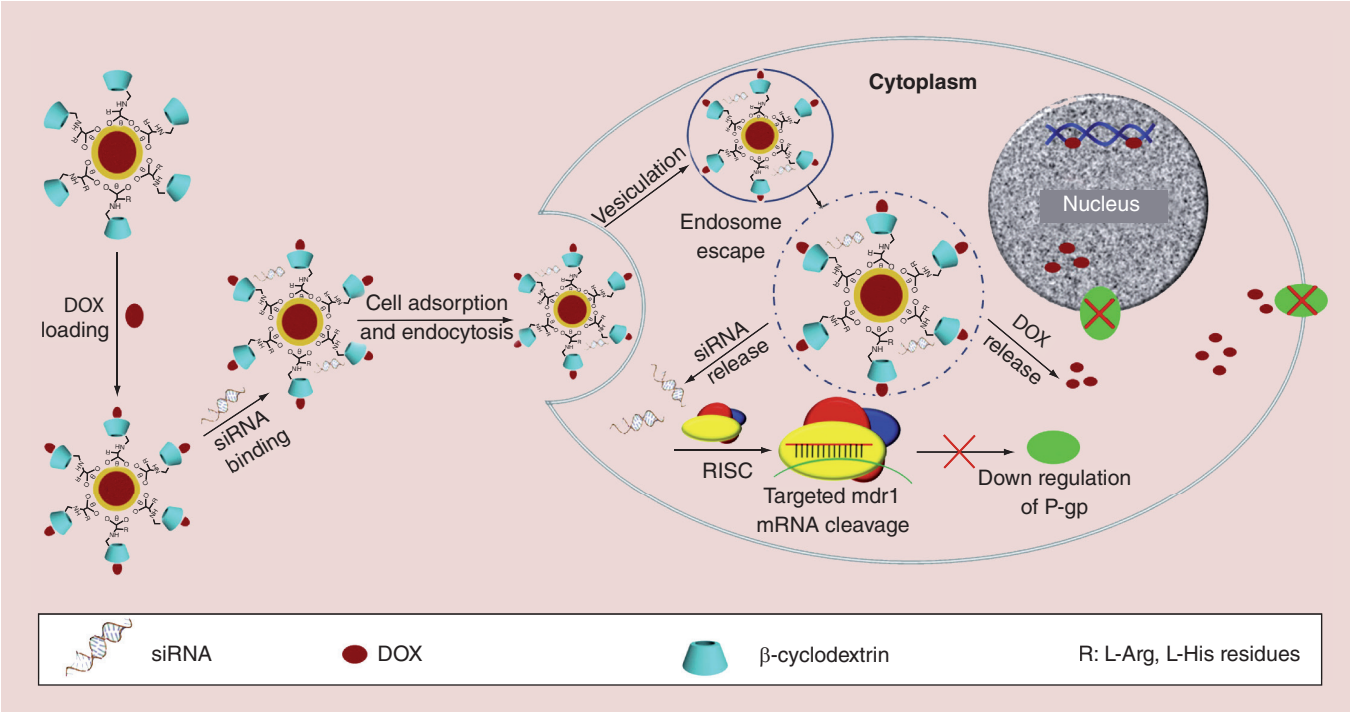

Figure 3. Schematic illustration of loading of doxorubicin and siRNA onto quantum dots functionalized with L-amino acids and β-cyclodextrin. The multifunctional quantum dots serve as codelivery platforms for siRNA and DOX to reduce drug resistance in cancer cells.
DOX: Doxorubicin.
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apoptosis of the cancer cells were both enhanced. The combined gene therapy and chemotherapy have great potential to destroy antidrug cancer cells.

Drug sequestration

Drug sequestration has also been achieved in supramolecular host–guest systems working as drug nanocontainers. Delivery of chemotherapy drugs faces two challenges: one is that the side effects cause the apoptosis of healthy cells, and the other is the short lifetime of cancer drugs in human body. Supramolecular host–guest systems have potential to overcome the challenges by sequestering drugs during transportation. For example, Adeli *et al.* developed polyrotaxane (PR) shells around gold nanoparticles to act as both drug nanocontainers and shields between drugs and healthy cells/tissues. The shells were constructed through the host–guest interaction between CDs and PEG, which noncovalently interacted with gold nanoparticles to form necklet-like nanostructures (Au NPs@PR) (Figure 4) [80]. Chemotherapy drugs such as Cisplatin and DOX conjugated with the PR shells were successfully sequestered. The photothermal properties of gold nanoparticles were used to cleave the shells for the release of the drugs via light activation.

Another strategy of the nanocontainer-based sequestering drugs was demonstrated by Rotello *et al.* [91]. As illustrated in Figure 5A, drug molecules (known as diaminohexanes) and CB[7]s were bonded together through host–guest interaction on gold nanoparticles. The capping of CB[7]s on diaminohexanes has reduced the cytotoxicity during transportation. Once delivered to target cancer cells, the orthogonal guest molecule, 1-adamantylamine, was added to dissemble the supramolecular host–guest systems and release drug to destroy the cancer cells. Scherman *et al.* employed a similar mechanism to develop cytotoxicity-switchable supramolecular nanosystems based on polymers functionalized with 2-naphthol via host–guest interaction between CB[8] and 2-naphthol (Figure 5B) [92]. The functionalized polymers cut off the contact between the environments and drug molecules, and the cytotoxicity was activated upon the addition of competitive binding molecules.

Protein immobilization

Protein immobilization on solid surfaces has captured great interests for both drug discovery [93,94] and other applications such as proteomic screens [95,96] and biomarker detection [97,98]. Supramolecular chemistry holds advantages in protein immobilization for its good responsiveness and reversibility [99,100]. In particular, supramolecular host–guest systems are a promising candidate for the surface-anchored

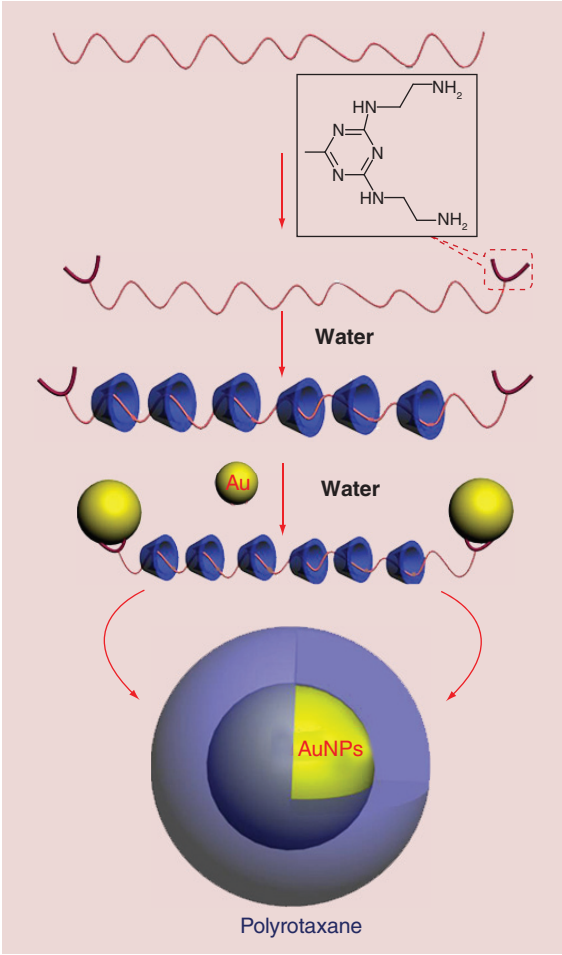

Figure 4. Schematic illustration of the synthetic processes for gold nanoparticles@polyrotaxane hybrid nanomaterials. The Au nanoparticles are functionalized with citrate shells so that the end triazine groups of polyrotaxanes can noncovalently interact with Au nanoparticles to form the necklet-like nanomaterials. AuNP: Gold nanoparticle.

protein assemblies because the cavities of host molecules form complexes with peptide motifs [101,102]. For example, Yang *et al.* [103] incorporated a ferrocene guest moiety into a protein to allow the protein immobilization within a β-CD host molecule on a gold surface.

Proteins have also been immobilized on SiO_2 nanoparticles [104]. For this purpose, naphthol guest molecules and MV guest molecules were encapsulated inside the host cavity of CB[8]s. The naphthol molecules were bonded with proteins and MV molecules were attached to the surfaces of SiO_2 nanoparticles. The immobilization of proteins on SiO_2 nanoparticles was reversible. The disassembly of the protein complexes was carried out by incubating the nanoparticles in a suspension of activated Zn powder in PBS, and the reinstallation of the immobilization was realized by immersion into a solution containing fresh CB[8]s and naphthol molecules.

As a summary, due to the available inner spaces in host molecules and the chemical affinity of host–guest molecules, supramolecular host–guest systems can function as nanocontainers for the *in vivo* deliver of drugs or other therapeutic materials. Compared with solid-state nanoparticles, the supramolecular nanocontainers have the potential to deliver the therapeutic agents in the more versatile way through the atomic-level tailoring of the physical size and the chemical affinity of the guest-host molecules. The unique properties of nanoparticles have further enhanced the flexibility of the hybrid nanoparticle–supramolecule systems in therapeutic delivery, including the targeted delivery with a modest magnetic field rather than the complex nanoparticle surface functionalization. Future research need be directed toward improving the loading capability of the host molecules with regard to the types and amount of therapeutic agents in order to meet the requirements of clinical applications.

Nanoparticles functionalized with supramolecular host–guest systems for sensing applications

High-sensitive, high-selective chemical and biological sensors are required for a broad range of applications in chemistry, biology, healthcare, medicine and the environments [105,106]. For instance, excessive use of chemicals such as pesticides, herbicides and spermines leave residues in agricultural products and the environments, putting human health under high risk. Sensors that can detect such chemicals with low concentration are of prime importance for the reduction of the risk. Nanoparticles functionalized with supramolecular host–guest systems are emerging as a new type of sensors for the detection of harmful substances in various samples. Compared with other sensors such as fluorescence spectroscopy [107,108], gas chromatography [109,110] and gas chromatography-mass spectrometry [111,112], the nanoparticle–supramolecule sensors have multiple advantages, including simple sample preparation, low cost and high sensitivity. In the following sub-sections, we review two types of sensors based on the nanoparticles functionalized with supramolecular host–guest systems, in other words, surface-enhanced Raman spectroscopy (SERS) and LSPR sensors.

Surface-enhanced Raman spectroscopy

Metal nanoparticles functionalized with supramolecular host–guest systems as SERS substrates have captured significant attentions [113]. SERS-based detection can identify molecular species with an extremely low concentration down to the single-molecule

level [114–119]. The SERS occurs to molecules located near the surfaces of nanostructures of noble metals such as gold, silver and copper where the excitation of surface plasmons generates high electromagnetic fields that enhance the light absorption and scattering by the molecules [120–125]. However, some molecules have low affinity toward metal surfaces and thus require molecular receptors to enhance their binding with metal nanostructures for SERS measurements.

Supramolecular host–guest systems on metal nanoparticles have provided a solution to the low affinity by trapping target molecules as guests within the host cavities. The target molecules, once captured by the host molecules on the metal nanoparticles, experience the highly concentrated electromagnetic fields for SERS. Strickland and Batt employed CD-functionalized gold nanorods for SERS detection of the inclusion complexes of carbendazim, a model benzimidazole fungicide [122]. Carbendazim with a low concentration of 50 μM was detected. In another example, CD-functionalized silver nanoparticles were employed as SERS substrates for the detection of hydrobenzoin, a molecule that has no affinity to silver [126]. Moreover, SERS has also been employed to help understand the pH-dependent formation of diquat-CB[n] host–guest molecular systems on silver nanoparticles [127].

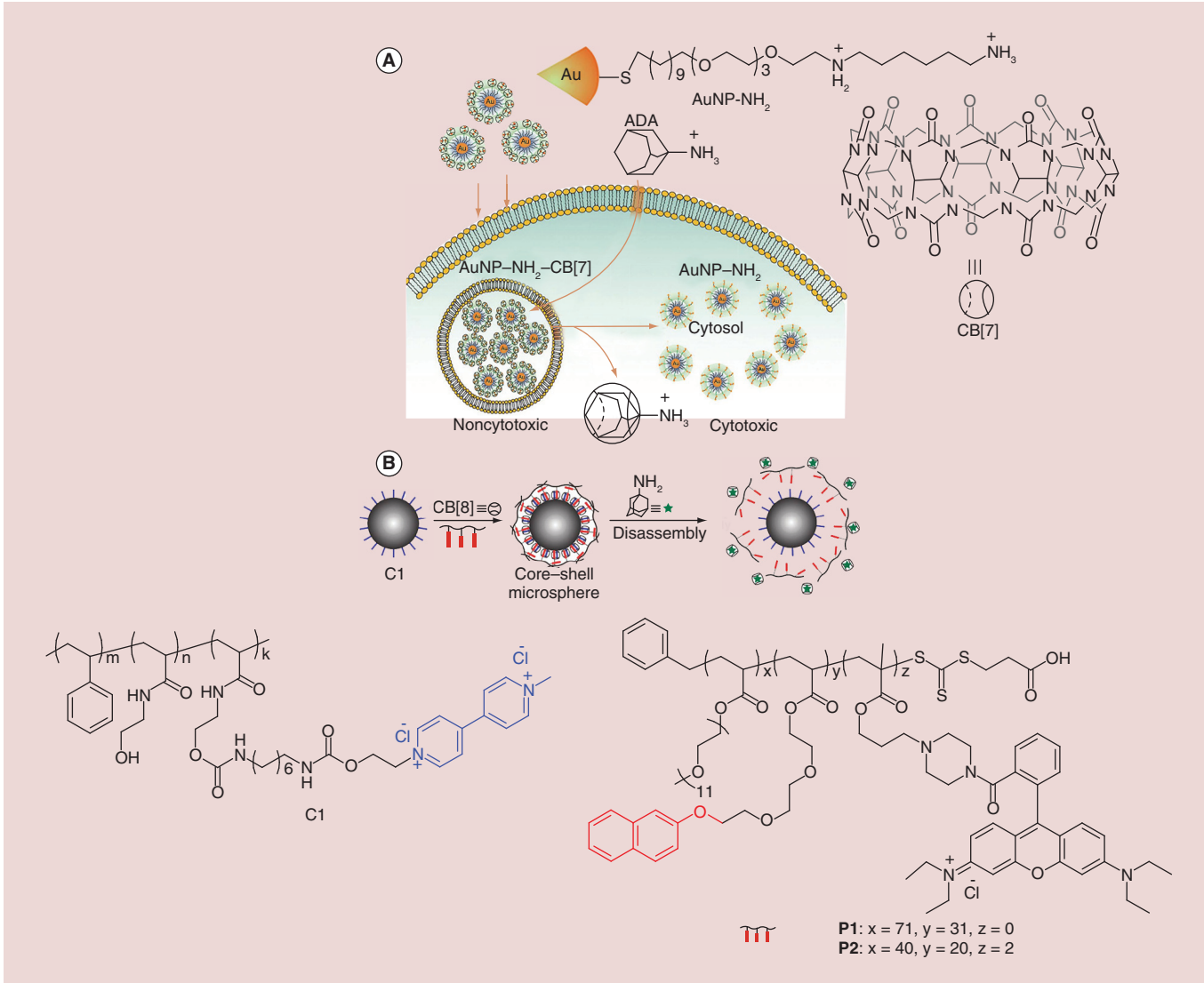

Figure 5. Schematic illustrations of drug sequestration via host–guest interactions between the drug molecules and cucurbit[7]urils on gold nanoparticles. **(A)** The capping of CB[7]s on drug molecules has reduced the cytotoxicity during transportation. **(B)** Schematic illustration of the preparation and disassembly of core–shell polymeric microspheres.
ADA: 1-adamantylamine; AuNP: Gold nanoparticle; CB[n]: Cucurbit[n]uril.
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One of the most significant progresses in SERS based on host–guest interactions is the demonstration of selective detection and quantitative analyses of specific components in mixture solutions. For example, Xie *et al.* demonstrated the SERS detection of five types of polycyclic aromatic hydrocarbon (PAH) molecules (i.e., ianthracene, pyrene, chrysene, triphenylene and coronene) based on the host–guest interaction between PAH and per-6-deoxy-(6-thio)-β-CD (CD-SH) on gold nanoparticles (Figure 6A) [43]. SERS spectra were recorded from the mixed PAH molecules with a low concentration of 10 μM (Figure 6B). It is worth noting that coronene molecules have the largest size among the PAH molecules and are not easily captured by CD-SHs, exhibiting no obvious enhancements of the Raman signals. Analyses of the SERS spectra provided the compositional information of the mixtures since each type of PAH molecule has its own Raman signals. More achievements include the quantitative SERS analysis of one component in the mixture of several types of PAH molecules. In the demonstration, the mixture was composed of chrysene, triphenylene and coronene with each concentration of 10 μM, together with anthracene and pyrene with different concentrations ranging from 500 to 50 μM. The intensities of SERS peaks of anthracene (Figure 6C) and pyrene (Figure 6D), which show consistent behavior with the changing concentration of these two components, have been interrogated to quantify the molecules.

The final goal for SERS is to achieve single-molecule detection with high reproducibility. SERS substrates based on nanoparticles functionalized with supramolecular host–guest systems are paving the way toward this goal. It has been shown that the narrow nanogaps among aggregates of metal nanoparticles with the significantly enhanced electromagnetic fields (known as 'hot' spots) are responsible for the single-molecule SERS [121,128–132]. However, most of the methods for preparation of the aggregates of gold [133] or silver [134] nanoparticles have remained challenging in both producing 'hot' spots with the uniform nanogaps and confining analytes within the 'hot' spots, which are required for the reproducible single-molecule measurements. A promising strategy to overcome this challenge is to introduce supramolecular host–guest systems on the metal nanoparticles.

Due to the capability of linking individual nanoparticles to form assemblies and of trapping guest molecules inside their cavities, macrocyclic host molecules on metal nanoparticles can precisely confine the analyte molecules into the 'hot' spots. For example, Li *et al.* developed cucurbit[n]urils on gold nanoparticles to induce aggregation of the nanoparticles with precisely defined nanogaps between the neighboring nanoparticles (Figure 7A) [135]. Ferrocene, an 'inert' molecule that does not adsorb on gold surfaces, was captured into the cavity of CB[7] and exposed to the intense electromagnetic fields in the 'hot' spots. As a result, the SERS enhancement factor for ferrocene was found to be up to 1.7×10^9 (Figure 7B). In addition, ferrocene trapped by CB[7] has no direct contact with gold surfaces, which provides a platform for mechanistic investigations of electromagnetic enhancements in SERS without the interference from chemical enhancements [136,137].

Recently, Mahajan *et al.* demonstrated the high-sensitive, quantitative SERS detection of multiple analyte molecules based on metal nanoparticles functionalized with supramolecular host–guest systems. As illustrated in Figure 8A, CB[8]s were employed as host molecules that captured two guest molecules to form ternary complexes [138]. The CB[8] was initially loaded with dicationic electron-deficient MV as the first guest. A variety of analyte molecules, including anthracene, 2-naphthol, phloroglucinol and 2,3-naphthalenediol, acted as the second guests. The Raman modes from the second guests can be identified in all the complex SERS measurements (Figure 8B). With binding isotherms calculated from the molar ratio of complex CB[8]s based on the SERS signal intensities, the single concentrations of 2-naphthol and 2,3-naphthalenediol were analyzed below 10 μM levels. The good match between the SERS results and the actual concentrations indicates that SERS based on the nanoparticle–supramolecule systems can quantitatively detect the nonfluorescent analyte molecules with ultra-sensitivity. The detection limit in this work reached a level of 10^{-11} M, which exceeded other published SERS methods by at least three orders of magnitude. This study depicts a new method to quantitatively detect small harmful molecules. It is also entirely possible that this method could also be extended to other types of target molecules through the rational design of host molecules and metal nanoparticles.

LSPR sensors

Monitoring changes in the LSPRs of metal nanoparticles due to the host–guest interactions has provided another sensing mechanism. LSPR-based colorimetric sensors have been realized when the spectral changes of LSPRs occur in the range of visible light induced by the assembly or disassembly of metal nanoparticles [139–141]. Figure 9 illustrates an early example of the LSPR sensors based on gold nanoparticle agglomeration via the host–guest interactions [142]. The gold nanoparticles (~12 nm in diameter) were functionalized with per-6-thio-β-CDs as host molecules. When the analyte molecules, ferrocene dimers, were added into the nanoparticle suspensions, they served as link-

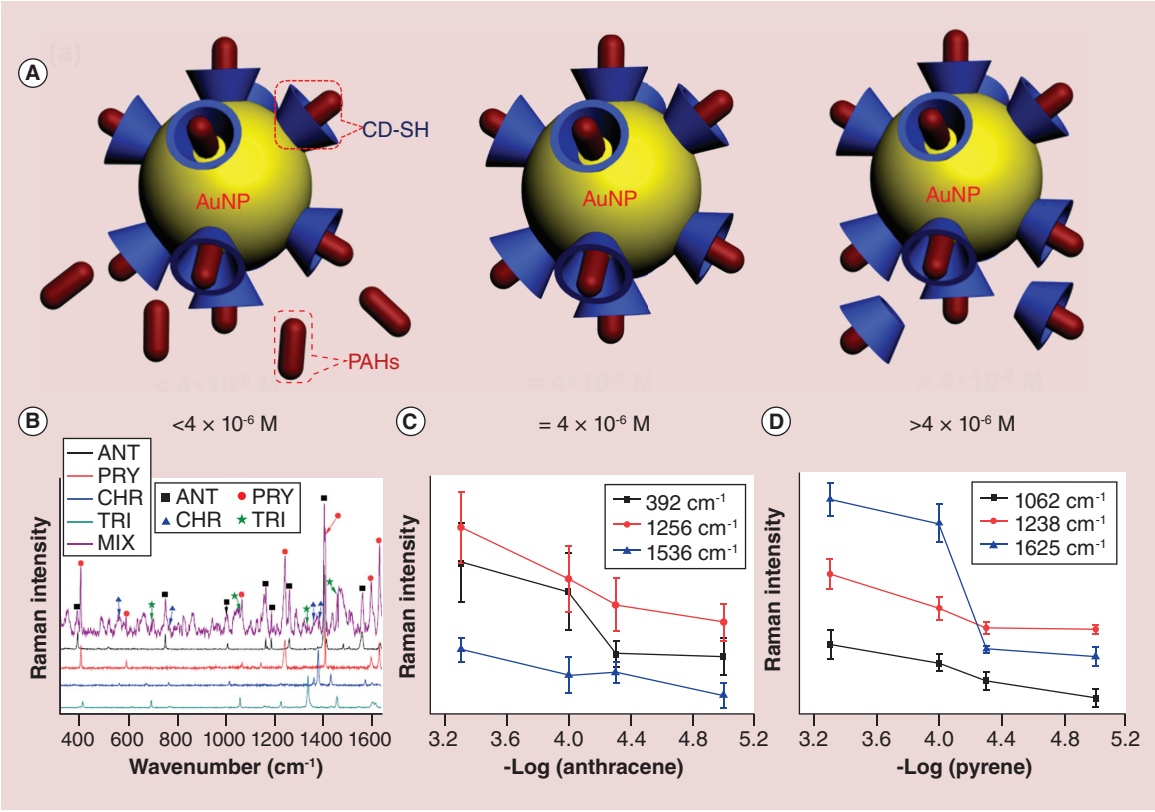

Figure 6. Nanoparticles functionalized with supramolecular host–guest systems for selective detection and quantitative analyses. **(A)** Schematic illustration of different scenarios for the host–guest interactions between PAHs and CD-SH on nanoparticles. **(B)** Surface-enhanced Raman spectroscopy spectra of individual and mixed PAHs. The concentration of each PAH was 10^{-5} M. **(C & D)** Intensities of surface-enhanced Raman spectroscopy modes as a function of concentration for **(C)** anthracene and **(D)** pyrene in the mixed PAHs. The concentrations of the other components were kept at 10^{-5} M.
ANT: Anthracene; AuNP: Gold nanoparticle; CD-SH: Per-6-deoxy-(6-thio)-β-cyclodextrin; CHR: Chrysene; MIX: Mixed PAHs; PAH: Polycyclic aromatic hydrocarbon; PRY: Pyrene; TRI: Triphenylene.
(B–D) Reproduced with permission from [43] © John Wiley and Sons (2010).

ers to induce aggregation of the nanoparticles via the host–guest interaction, leading to a large redshift in the LSPR spectra of the gold nanoparticles.

Tremendous progress has been made in applying metal nanoparticles functionalized with supramolecular host–guest systems for the detection of various analytes based on the analyte-induced aggregation of the nanoparticles and the resulted changes in the LSPRs. The analytes include pesticides, amino acids, aromatic compounds and enzymes [27,143–145]. For example, the host–guest interactions between paraquats and CP[5]A on gold nanoparticles have been utilized to detect paraquat, one of the most commonly used herbicides (Figure 10A) [146]. The changes in color (Figure 10B) and UV/Vis absorption spectra (Figure 10C) of the nanoparticle solutions with different paraquat concentrations enabled the real-time, sensitive and quantitative measurement of the herbicides with a detection limit as low as 0.2 μM. It is worth noting that, besides metal nanoparticles, CdTe quantum dots have also been functionalized with CP[5]A for the development of herbicide sensors based on the aggregation of quantum dots via the host–guest interactions between CP[5]A and herbicide molecules [147].

While most of the LSPR sensors have been based on the analyte-induced aggregation of nanoparticles, the disassembly process has been harnessed for the detection of enzymes. As demonstrated by de la Rica *et al.*, the aggregates of β-CD-functionalized gold nanoparticles with diFc as linker were disassembled by enzyme, known as horseradish peroxidase (HRP), through the biocatalytic oxidation of diFc [148]. Measuring the changes in LSPRs of gold nanoparticles induced by this disassembly process enabled the detection of HRP with concentrations of 0.001–0.1 pg/ml. With the incorporation of another type of guest molecule known as Ad-PEG, which promoted the disassembly of gold nanoparticle aggregates through competitive interactions with β-CDs, the detection limit was improved to approximately 23 HRP molecules.

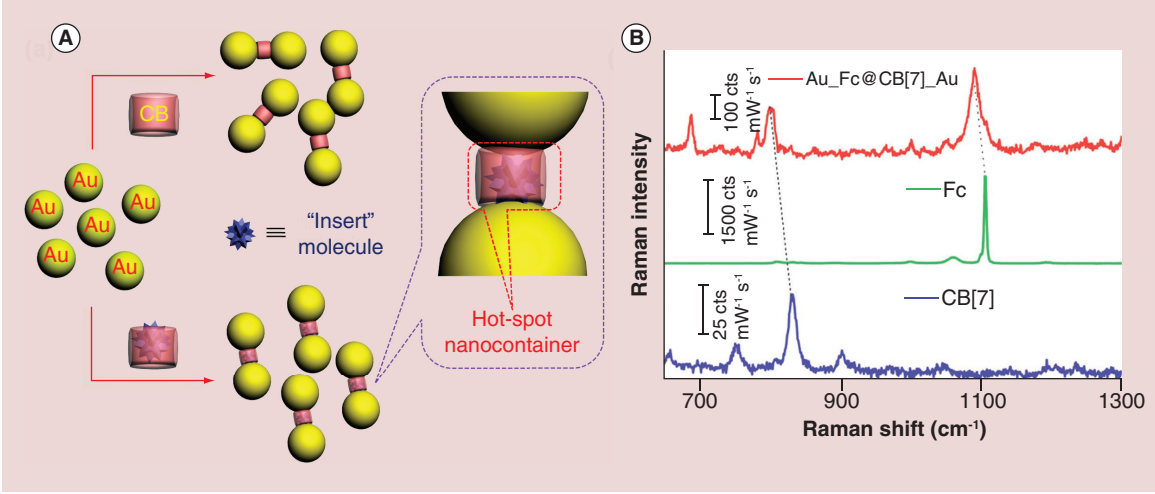

Figure 7. Nanoparticles functionalized with supramolecular host–guest systems for single-molecule trapping and detection. **(A)** Schematic representation of the formation of SERS 'hot' spots with and without analyte molecules by bridging gold nanoparticles via CB[n] macrocyclic host molecules; **(B)** Raman spectra recorded from gold nanoparticle aggregates bridged with CB[7] and Fc (red curve), bulk Fc (green curve) and bulk CB[7] (blue curve). CB[n]: Cucurbit[n]uril; Fc: Ferrocene.
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The rational design of nanoparticles and supramolecular host–guest systems has enabled versatile control in the shapes and sizes of nanoparticle aggregates. For example, Qi *et al.* applied the host–guest interaction between toluene molecules and α-CDs on gold nanoparticles to achieve the nanochains of gold nanoparticles [149]. Grzybowski and Stoddart *et al.* developed a template-directed self-assembly method to form dimers, trimmers and tetramers of gold nanoparticles [150]. The host–guest interactions between cyclobis(paraquat-*p*-phenylene)-based derivatives and the diethyleneglycol-disubstituted tetrathiafulvalene were tuned for the directed assembly. With their precisely controllable optical and electrical properties, these low-dimensional aggregates will pave the ways toward new or enhanced sensors and other applications.

As illustrated in this section, the integration of the response of host–guest supramolecular systems and the signal transduction of metal nanoparticles leads to the enhanced selectivity and sensitivity of SERS- and LSPRs-based optical sensors. The selectivity benefits from the specificity of the host–guest interactions. The sensitivity arises from the capability of trapping target molecules at the surfaces of nanoparticles where the plasmonic enhancements of electromagnetic fields are maximal. Both SERS and LSPRs have been heavily studied for applications in nanomedicine and healthcare, including the early disease diagnosis and the detection of trace amount of pollutants in solutions. With the supramolecular enhancement, the optical sensors are getting closer to the clinical applications and the practical environmental protections. With the modification of surface chemistry, the host–guest systems can also be applied to other types of sensors such as those based on magnetic and electrical properties of nanoparticles for the enhanced performance.

Nanoparticles functionalized with supramolecular host–guest systems for removal of harmful substances

High-efficient, high-throughput and high-purity removal of harmful substances from aqueous solutions helps improve the environmental protection and food safety. The nanoparticles functionalized with the host–guest supramolecular systems have exhibited tremendous advantages for the applications because of their dual functions of sensing and separating the harmful substances from the aqueous environments [151]. The separating process occurs via the effective capture of target molecules by macrocyclic host compounds immobilized on nanoparticles followed by the natural sedimentation of the nanoparticle complexes, the removal of the complexes by external forces, or the nanoparticle-enhanced catalytic degradation of the target molecules. Progresses have been made in both supramolecules and nanoparticle–supramolecule systems to achieve effective removal of harmful molecules from solutions.

Saad *et al.* prepared sorbent materials based on crown ethers to selectively extract biogenic amines by batch sorption method [152]. In their demonstration, the sorbent materials were equilibrated with a mixture of five biogenic amines, including histamine, putrescine, tryptamine, tyramine and sperdimine. The highest selectivity of these crown ethers toward sperdimine enabled the extraction of this specific amine from the mixture. Recently, Yang *et al.* extracted parabens

from red wine samples using CP[5]As-functionalized poly(GMA-co-EDMA) via strong interaction between the paraben and the cavity of CP[5]A [153].

Chalasani and Vasudevan designed magnetic Fe_3O_4 nanoparticles functionalized with β-CDs to remove pollutants from water using magnetic force [154]. Specifically, the Fe_3O_4 nanoparticles functionalized with carboxymethyl-β-cyclodextrin captured PAH molecules in solutions. The nanoparticle complexes were removed from the solutions by applying a low magnetic field (0.5 T). Other similar examples include the use of Fe_3O_4 nanoparticles functionalized with carboxymethyl-β-cyclodextrin or CP[5]As for removal of As ions, Pb(II), and other pesticides (including 2-naphthol) from water and commercial beverage samples such as wines and orange juice [155,156].

Nanoparticle-enhanced degradation of harmful substance has been demonstrated based on the macrocyclic host molecules on photocatalytic nanoparticles. For example, Vasudevan and Chalasani prepared CD-functionalized Fe_3O_4@TiO_2 magnetic core-shell nanoparticles to photodegrade endocrine-disrupting chemicals, bisphenol A and dibutyl phthalate, which are hazardous chemical substances in water [157]. The anchored CDs provided the hydrophobic cavities for the capture of these two pollutants via host–guest interaction, which allows the pollutant molecules to come close enough to the surface of the TiO_2 shell. Under UV illumination, the photocatalytic property of TiO_2 causes the degradation and mineralization of the two pollutants. It is worth noted that once the photocatalytic degradation is complete, the magnetic core-shell nanoparticles can be completely separated from the solution by applying modest magnetic field for the further applications.

In summary, macrocyclic host molecules immobilized on nanoparticles have multiple advantages for the removal of harmful substances from aqueous solutions. Compared with the well-developed solid-phase extraction methods, the nanoparticle–supramolecule systems exhibit the higher efficiency and purity. The advantages benefit from the synergistic integration of the sensing and trapping capabilities of host molecules toward target molecules and the large surface areas and the controllability of nanoparticles. The demonstration of photocatalytic degradation of pollutants on nanoparticle–supramolecule systems paves the way toward the large-scale water cleaning and environmental protection with solar irradiations.

Conclusion

Integrated nanosystems that interface supramolecular host–guest systems with nanoparticles open up a new window of opportunities for the enhanced or

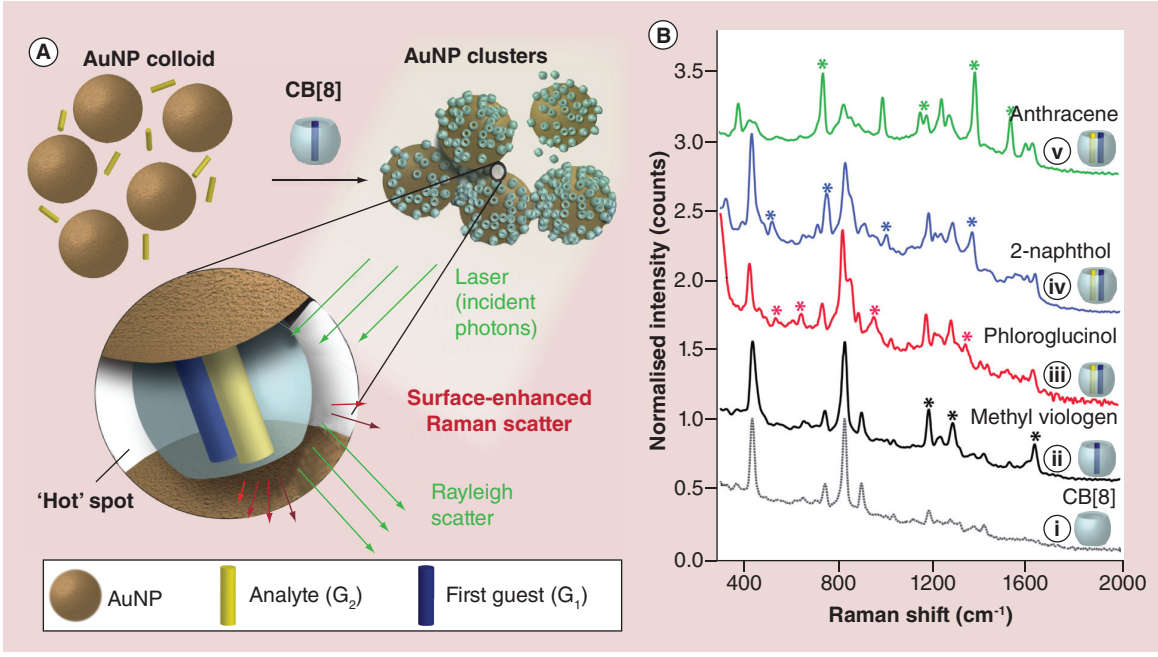

Figure 8. Nanoparticles functionalized with supramolecular host–guest systems for high-sensitive, quantitative surface-enhanced Raman spectroscopy detection. (A) Schematic representation of elastic (Rayleigh) and inelastic (surface-enhanced Raman spectroscopy) light scattering from analyte molecules encapsulated in CB[8] host molecules within the 'hot' spots of the aggregated gold nanoparticles. **(B)** Surface-enhanced Raman spectroscopy spectra of **(i)** CB[8] and **(ii–v)** CB[8]-analyte complexes.
AuNP: Gold nanoparticle; CB[n]: Cucurbit[n]uril.
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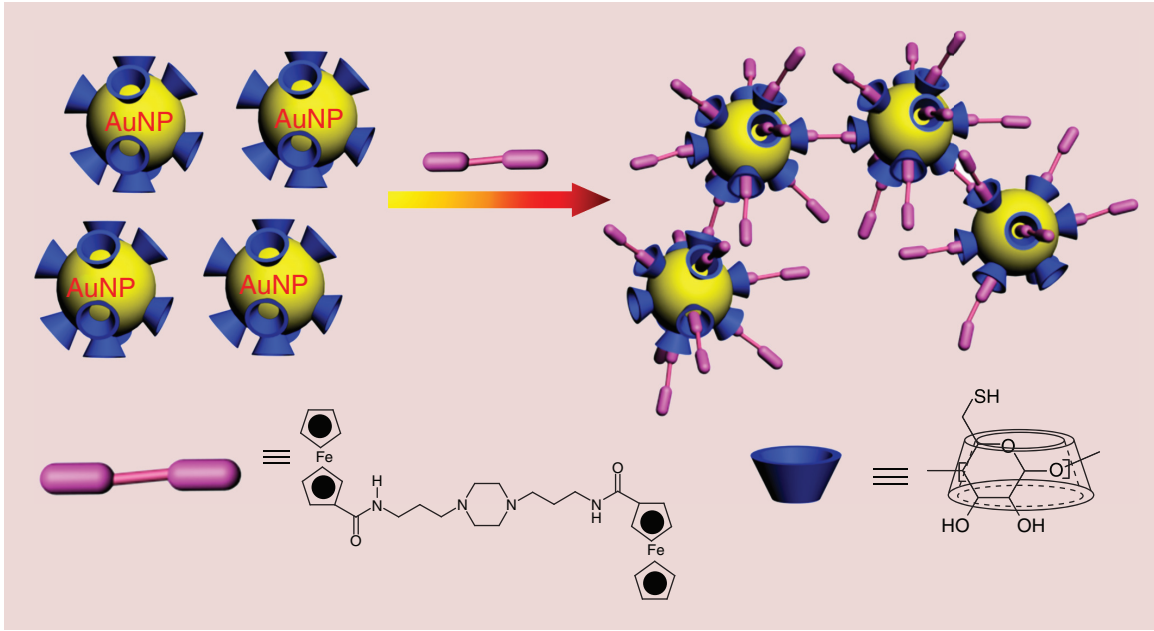

Figure 9. Schematic illustration of the aggregation of gold nanoparticles through the supramolecular host–guest interaction between ferrocene and cyclodextrin. The ferrocene dimers link two adjacent gold nanoparticles to form aggregates.
AuNP: Gold nanoparticle.

novel applications in nanomedicine and healthcare. Tremendous progress has been made in designing and applying nanoparticles functionalized with supramolecular host–guest systems in therapeutic delivery, sensing and removal of harmful substances from aqueous environments. The supramolecular host–guest systems that function as nanogatekeepers or nanocontainers for the nanoparticle-based therapeutic delivery have enabled precise, on-demand delivery of drugs and proteins at the target cells and tissues. The developments of dual activation and sequence activation have paved way toward therapeutic delivery systems with improved precision and release profiles for enhanced therapy with low side effects and have provided new solutions to the more complicated diseases. Based on SERS and LSPR spectroscopy, nanoparticles functionalized with supramolecular host–guest systems have shown great potential for real-time, high-sensitive, high-selective detection of a broad range of analyte molecules. The dramatic changes in LSPRs of metal nanoparticles upon their assembly or disassembly have allowed colorimetric detection of analyte molecules. The capability of capturing and trapping guest molecules in the cavities of host molecules immobilized on nanoparticles, in combination with the separation of the complexes from solutions or the nanoparticle-enhanced catalytic degradation of the guest molecules, has enabled the removal of harmful substances from aqueous environments such as water and beverages.

Future perspective

Despite their tremendous success, nanoparticles functionalized with supramolecular host–guest systems are still at the very early stage for practical applications in nanomedicine and healthcare. Many problems have to be solved before these integrated nanosystems can be fully implemented in a broad range of applications. For example, in therapeutic delivery applications, an enhanced targeting accuracy is significant for increased therapeutic efficiency with reduced side effects. However, it has remained challenging to develop surface chemistry on nanoparticles that enables both high targeting accuracy and smart drug release. In many cases, the targeting molecules and the host–guest supramolecules interference with each other, resulting in the deteriorated functions. Moreover, with the enhanced complexity in structures and functions, nanoparticles functionalized supramolecular host–guest systems require the more detailed evaluation of their biocompatibility and fate in human body. For the sensing applications, one need further enhance the design and control of host–guest interactions to achieve high-selective and high-sensitive detection of target molecules. In the SERS based on the supramolecule-nanoparticle nanosystems, signal interference from the host molecules could be an issue for analyte molecules that have similar Raman signatures to the host molecules. Practical use in removal of harmful substances from the large-scale aqueous environments requires the mass production of nanoparticles functionalized with

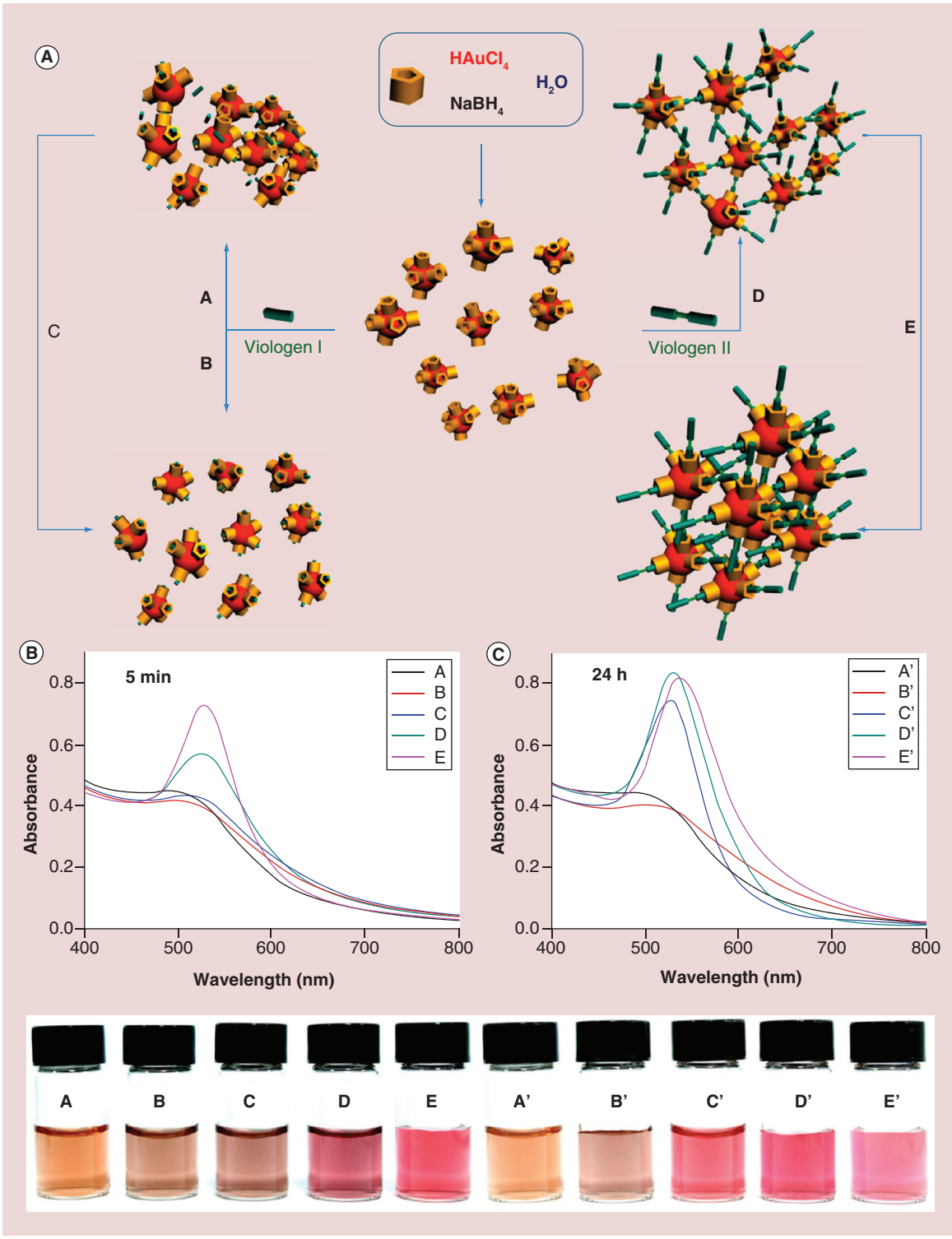

Figure 10. Analyte-induced aggregation of the nanoparticles functionalized with supramolecular host–guest systems for detection of analytes. (A) Schematic representation of the formation of carboxylatopillar[5]arene (CP[5]A)-modified gold nanoparticles and their aggregation upon addition of two types of viologen guest molecules; **(B)** UV-Vis spectra of CP[5]A-stabilized gold nanoparticles measured 5 min after the addition of viologen I with different concentrations: (A–E) 0, 5, 10, 15 and 75 μM. **(C)** UV-Vis spectra of CP[5]A-stabilized gold nanoparticles measured 24 h after the addition of viologen I with different concentrations: (A'–E') 0, 5, 10, 15 and 75 μM. Corresponding photographs of the solutions are shown below.
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supramolecular host–guest systems and the effective removal of the resulted nanoparticle complexes, which have not been achieved yet.

These problems in the supramolecule-nanoparticle systems for nanomedicine and healthcare are highly interdisciplinary in nature. Therefore, multidisciplinary approaches are needed in order to find solutions to these problems. Herein, we point out three directions for the future developments. First, molecular assembly and measurements on curved and faceted surfaces in order to precisely control the interactions between host–guest supramolecules and targeting molecules on single nanoparticles for the optimal performances in both targeting and drug release [158–160]. Second, the further research efforts in nanotoxicology are expected to help provide new insights into the biocompatibility of nanoparticle–supramolecule nanosystems in complicated, real clinical environments. The improved fundamental understanding of the interactions of nanoparticle–supramolecule nanosystems with tissues, cells and sub-cellular matters is expected in order to guide the rational design of nanoparticles and supramolecules for *in-vivo* applications. Lastly, the further progress in nanofabrication and chemical synthesis is required to allow the low-cost, high-throughput fabrication of nanoparticles with the desired shapes, sizes and functions. With the coordinated efforts from researchers in multiple disciplines, including engineering, physics, chemistry, biology and medicine, the emerging field of nanoparticles functionalized with supramolecular host–guest systems will make great strides and pave the way toward practical applications.

Financial & competing interests disclosure

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Executive summary

Background

- Macrocyclic host molecules such as crown ethers, calixarenes, cucurbit[n]urils, cyclodextrins, cyclophanes and pillarenes can capture guest molecules inside their cavities to form supramolecular host–guest systems. Interfacing supramolecular host–guest systems with nanoparticles leads to a new type of functional nanomaterials and nanosystems.
- Nanoparticles functionalized with supramolecular host–guest systems have been utilized for a wide range of applications in nanomedicine and healthcare, including therapeutic delivery, sensing and removal of harmful substances. For therapeutic delivery, the supramolecules function as either nanogatekeepers or nanocontainers.

Supramolecular host–guest systems as nanogatekeepers on mesoporous nanoparticles for therapeutic delivery

- Supramolecular host–guest systems on mesoporous silica nanoparticles (MSNs) work as nanogatekeepers to enable precise, on-demand release of drug molecules from the pores of MSNs.
- Nanogatekeepers have been structured into ten categories according to the activation methods, in other words, redox, UV light, pH, competitive binding, enzymatic, ultrasound, magnetic field, near infrared, sequential and dual.

Supramolecular host–guest systems as nanocontainers on nonporous nanoparticles in therapeutic delivery

- Drug molecules captured by the cavities of host molecules immobilized on nanoparticles have enabled on-demand released of drug at target tissues and cells.
- Drug molecules have been loaded into the cavities of host molecules or between the host–guest molecules and nanoparticles for sequestration. The sequestration of drugs has significantly reduced the side effects on the healthy cells during their transportation to the target tissues and cells.
- Immobilization of proteins on nanoparticles has been realized via host–guest interactions. The nanoparticle-bound proteins have shown potential applications in drug discovery, proteomic screens and biomarker detection.

Nanoparticles functionalized with supramolecular host–guest systems for sensing applications

- Metal nanoparticles functionalized with supramolecular host–guest systems have served as surface-enhanced Raman spectroscopy substrates for the high-sensitive, quantitative detection of analyte molecules.
- Localized surface plasmon resonances sensors have led to colorimetric detection of analyte molecules based on the analyte-induced assembly or disassembly of the supramolecule-functionalized nanoparticles.

Nanoparticles functionalized with supramolecular host–guest systems for removal of harmful substances

- Removal of harmful residues in water and beverages has been achieved through capturing the residue molecules inside the cavities of host molecules immobilized on nanoparticles followed by degradation of the residues or removal of the nanoparticle complexes.

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