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Macrocyclic Supramolecular Assemblies Based on Hyaluronic Acid and Their Biological Applications

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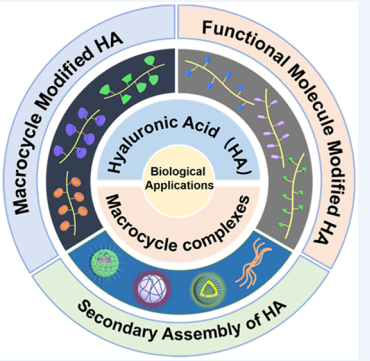
CONSPECTUS: Hyaluronic acid (HA), which contains multiple carboxyl, hydroxyl, and acetylamino groups and is an agent that targets tumors, has drawn great attention in supramolecular diagnosis and treatment research. It can not only assemble directly with macrocyclic host−guest complexes through hydrogen bonding and electrostatic interactions but also can be modified with macrocyclic compounds or functional guest molecules by an amidation reaction and used for further assembly. Macrocycles play a main role in the construction of supramolecular drug carriers, targeted imaging agents, and hydrogels, such as cyclodextrins and cucurbit[*n*]urils, which can encapsulate photosensitizers, drugs, or other functional guest molecules via host−guest interactions. Therefore, the formed supramolecular assemblies can respond to various stimuli, such as enzymes, light, electricity, and magnetism for controlled drug delivery, enhance the luminescence intensity of the assembly, and improve drug loading capacity. In addition, the nanosupramolecular assembly formed with HA can also improve the biocompatibility of drugs, reduce drug toxicity and side effects, and enhance cell permeability; thus, the assembly has extensive application value in biomedical research. This Account mainly focuses on macrocyclic supramolecular assemblies based on HA, especially their biological applications and progress in the field, and these assemblies include (i) guest-modified HA, such as pyridinium-, adamantane-, peptide-, and other functional-group-modified HA, along with their cyclodextrin and cucurbit[*n*]uril assemblies; (ii) macrocycle-modified HA, such as HA modified with cyclodextrins and cucurbit[*n*]uril derivatives and their assembly with various guests; (iii) direct assembly between unmodified HA and cyclodextrin- or cucurbit[n]uril-based host−guest complexes. Particularly, we discussed the important role of macrocyclic host−guest complexes in HA-based supramolecular assembly, and the roles included improving the water solubility and efficacy of hydrophobic drugs, enhancing the luminescent intensity of assemblies, inducing room temperature phosphorescence and providing energy transfer systems, constructing multi-stimulus-responsive supramolecular assemblies, and *in situ* formation of hydrogels. Additionally, we believe that obtaining in-depth knowledge of these HA-based macrocyclic supramolecular assemblies and their biological applications encompasses many challenges regarding drug carriers, targeted imaging agents, wound healing, and biomedical soft materials and would certainly contribute to the rapid development of supramolecular diagnosis and treatment.



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2. Zhou, W. L.; Chen, Y.; Yu, Q.; Zhang, H.; Liu, Z. X.; Dai, X. Y.; Li, J. J.; Liu, Y. Ultralong purely organic aqueous phosphorescence supramolecular polymer for targeted tumor cell imaging. *Nat. Commun.* **2020**, *11*, 4655.[2] CB[8] can encapsulate the 4-(4-bromophenyl)-pyridinium units grafted on HA to form supramolecular polymers, inducing purely organic room temperature phosphorescence in aqueous solution and successfully applying mitochondrial-targeted phosphorescence imaging in cancer cells.
3. Tang, M.; Song, Y.; Lu, Y. L.; Zhang, Y. M.; Yu, Z.; Xu, X.; Liu, Y. Cyclodextrin-activated porphyrin photosensitization for boosting self-cleavable drug release. *J. Med. Chem.* **2022**, *65*, 6764−6774.[3] Permethyl-*β*-cyclodextrin-modified HA specifically encapsulates porphyrin-modified prodrugs to improve fluorescence intensity and

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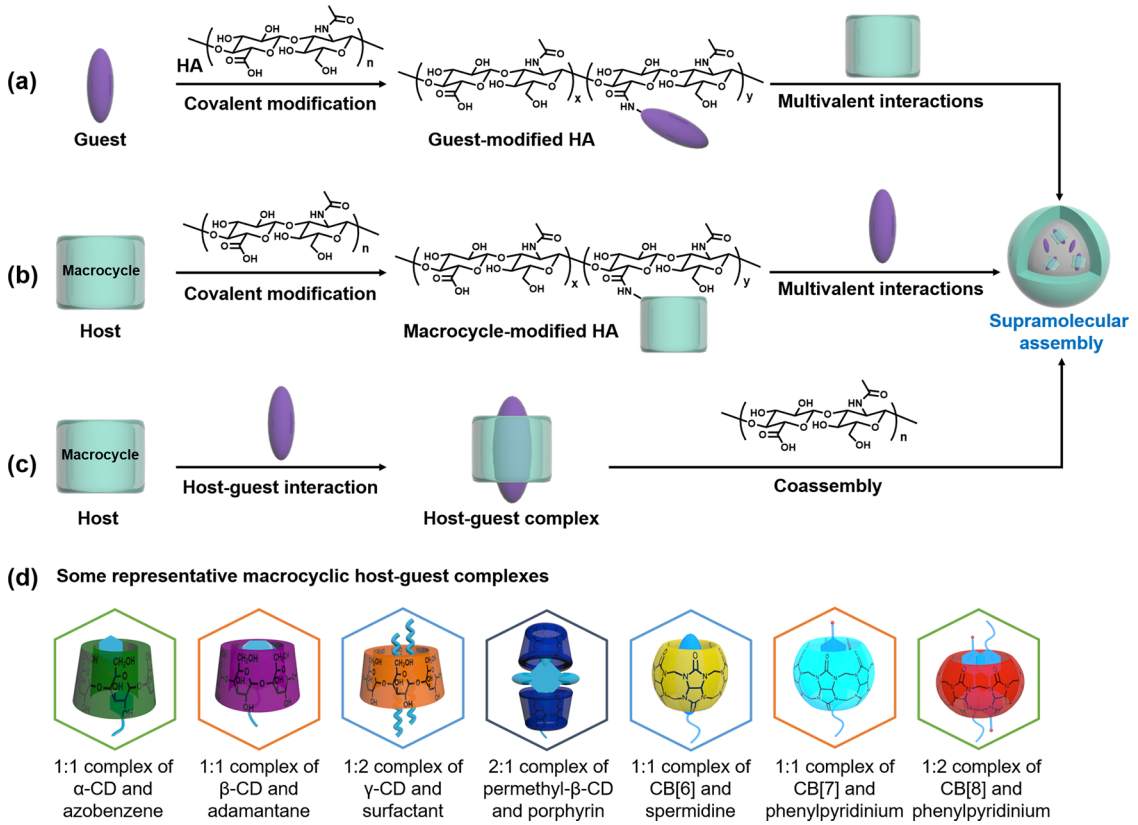
Scheme 1. Schematic Illustration of HA-Based Macrocyclic Supramolecular Assemblies[a]



[a](a) Guest-modified HA; (b) macrocycle host-modified HA; (c) direct assembly of HA with host−guest complexes; (d) some representative macrocyclic host−guest complexes in HA-based macrocyclic supramolecular assemblies and their stoichiometric ratios.

enhance $^1O_2$ generation efficiency through host−guest interaction, thereby not only promoting self-cleaving drug release but also effectively synergistically inhibiting tumor growth.

4. Dai, X. Y.; Zhang, B.; Yu, Q.; Liu, Y. *In situ* coassembly induced mitochondrial aggregation activated drug-resistant tumor treatment. *J. Med. Chem.* **2022**, *65*, 7363−7370.[4] Mitochondrial-targeting peptide and 4-bromophenylpyridium comodified HA can form a supramolecular assembly with CB[8] through host−guest complexation, induce *in situ* aggregation of mitochondria in cancer cells, and boost antitumor efficacy of cisplatin from 43 to 96% with self-reported green phosphorescence.

1. INTRODUCTION

Macrocyclic supramolecular assemblies that are based on hyaluronic acid (HA) have drawn great attention in several fields, including drug delivery,[5−8] molecular recognition and bioimaging,[9,10] hydrogels,[11−13] and cellular and tissue engineering fields.[14,15] In the process of constructing HA-based macrocyclic supramolecular assemblies, macrocyclic compounds play a key role, and these compounds can encapsulate photosensitizers, drug molecules, and other size-matched molecules through host−guest interactions to form multifunctional supramolecular assemblies.[16−18] Taking advantage of the tumor cells' targeting ability and good biocompatibility of HA, the coassembly of macrocyclic host−guest complexes with HA can not only target tumor cells but also enhance the biocompatibility and stability of the assemblies due to the multivalent interactions, thereby expanding their biological applications.[19−21] As a significant component of an extracellular matrix, HA is a water-soluble, biocompatible, and biodegradable linear polysaccharide that contains alternating repeating disaccharide units, *β*-1,4-D-glucuronic acid−*β*-1,3-*N*-acetyl-D-glucosamine, possessing multiple carboxyl, hydroxyl, and acetylamino groups.[22,23] HA can specifically bind some overexpressed receptors (e.g., cluster determinant 44 (CD44) and HA-mediated motor receptor (RHAMM) also known as CD168) on the surfaces of various cancer cells, realizing receptor-mediated endocytosis, which displays widespread applications in drug delivery systems.[24−26] Moreover, HA has important therapeutic roles in angiogenesis and macrophage polarization, which can be used in wound healing dressings and biomaterials approaches to treating infarction, brain injury, and so on.[27−29] Therefore, the coassembly of HA and macrocyclic host−guest complexes functions as an excellent drug carrier and has a role in supramolecular diagnosis and treatment research, targeted imaging, injectable hydrogels, and bioscaffolds.

In addition to directly assembling with host−guest complexes through multiple hydrogen bonding and electrostatic interactions,[30] HA can also be modified with macrocyclic compounds (e.g., cyclodextrins (CDs),[31] cucurbit[*n*]urils (CB[*n*]s)[32]) or functional guest molecules (e.g., pyridinium,[33] adamantane,[34] and peptide[35]) through amidation to form multifunctional biomacromolecules for further assembly. CDs are macrocyclic oligosaccharides linked by D-glucose through *α*-1,4-glycosidic bonds, and the commonly used CDs contain

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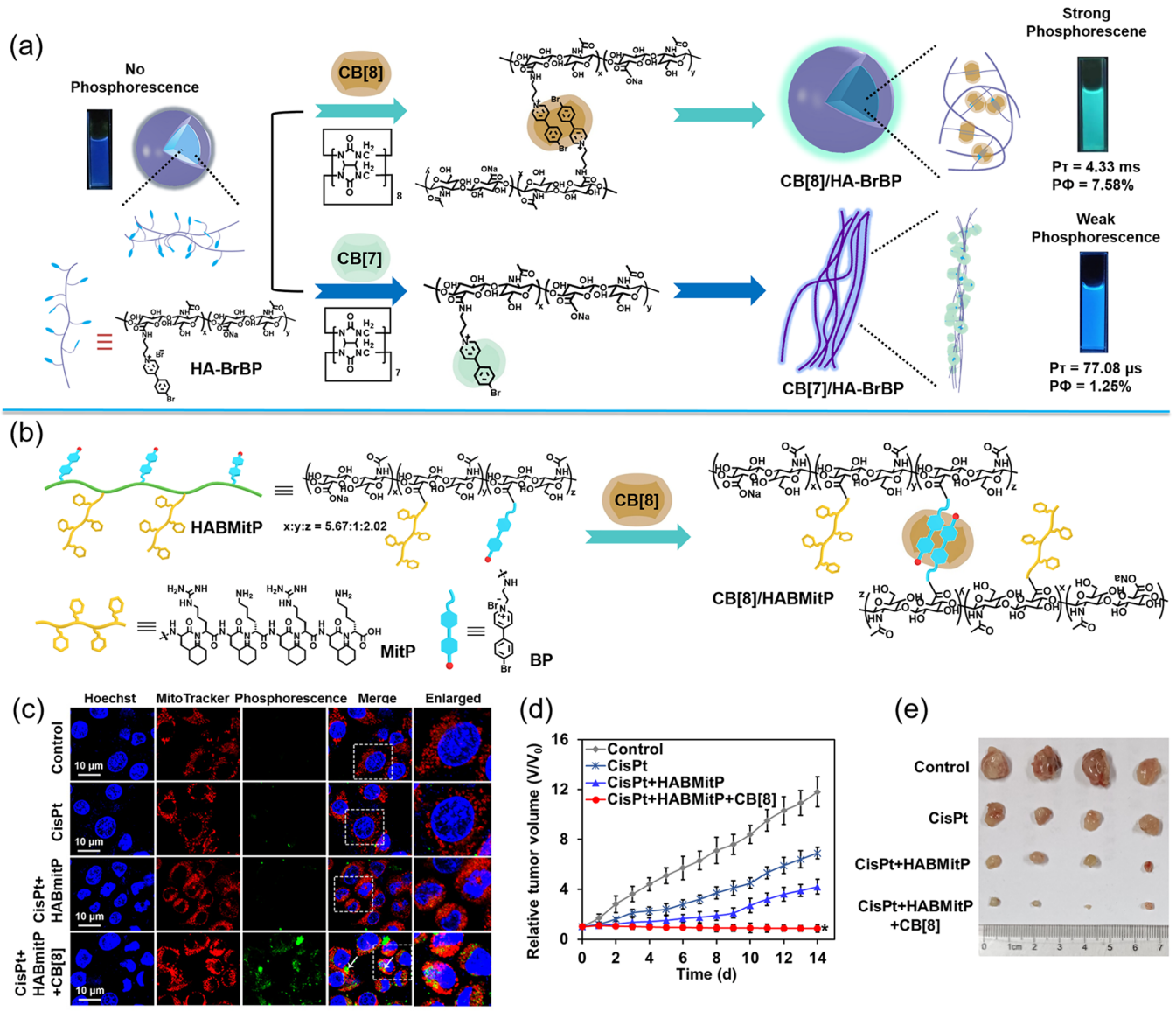

Figure 1. (a) Schematic illustration of phosphorescent supramolecular assemblies of CB[8]/HA−BrBP and CB[7]/HA−BrBP; the BrBP unit in HA−BrBP forms 1:1 and 2:1 complexes with CB[7] and CB[8], respectively. Reproduced with permission from ref 2. Copyright 2020 The Authors. (b) Schematic illustration of a multivalent supramolecular polymer of CB[8]/HABMitP; the BP unit in HABMitP forms a 2:1 complex with CB[8]. Reproduced with permission from ref 4. Copyright 2022 American Chemical Society. (c) Mitochondrial morphology changes in cisplatin-resistant tumor cells treated with CisPt, CisPt+HABMitP, and CisPt+HABMitP+CB[8]. Reproduced with permission from ref 4. Copyright 2022 American Chemical Society. (d) Tumor volume in mice treated with cisplatin-resistant tumors. Reproduced with permission from ref 4. Copyright 2022 American Chemical Society. (e) Tumor photos of treated mice. Reproduced with permission from ref 4. Copyright 2022 American Chemical Society.

six, seven, and eight D-glucose units, which are named α-, β- and γ-CD, respectively.[36−38] Due to the different cavity volumes, CDs can encapsulate different kinds of size-matched guest molecules through hydrophobic interactions.[39−41] CB[n]s are formed by condensation of glycoluril with formaldehyde under the condition of acid catalysis and contain a robust skeleton, a hydrophobic cavity, and two identical ports filled with carbonyl groups.[42,43] The commonly used CB[n]s are CB[6], CB[7], and CB[8], which can not only provide potential inclusion sites for nonpolar molecules but also bind cationic guests via ion−dipole interactions with carbonyl groups.[44−46] In terms of the interaction between macrocycle host and functional guest, the association constant is important in the process of self-assembly and release,[47−49] which directly affects the time frame of drug release, such as a photocontrolled system for different association constants of *trans*- and *cis*-azobenzene with cyclodextrin and the stability of a formed polymer−polymer hydrogel system through multivalent interactions.[50−52] With the aid of specific macrocycle host−guest, hydrophobic, and electrostatic interactions, many functional guests can be integrated into supramolecular assemblies; the formed host−guest complexes not only endow the assemblies with a responsiveness to multiple stimuli (e.g., enzymes, light, electricity, magnetism) but also enhance the luminescence intensity of molecules and improve the loading of drugs.[53−55] On the other hand, the nanosupramolecular assembly formed with HA can also improve its biocompatibility, reduce drug toxicity and side effects, and

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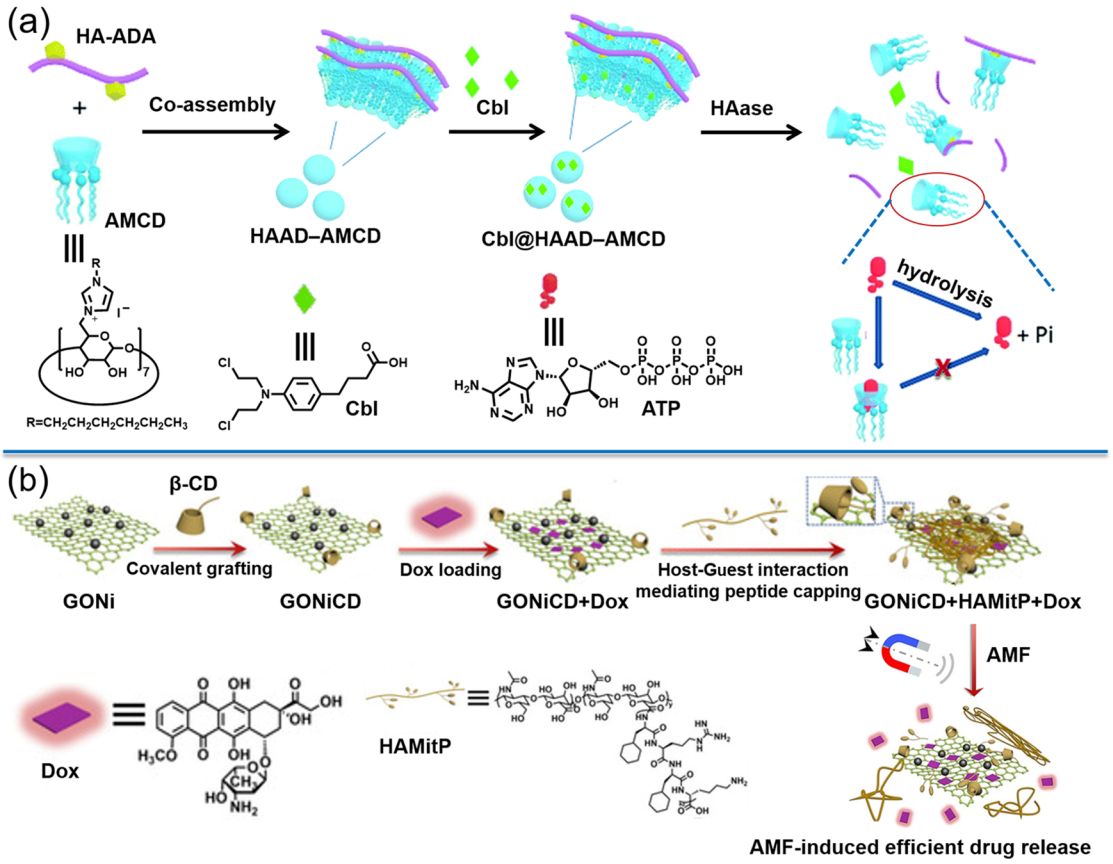

Figure 2. (a) Schematic illustration of Cbl-loaded assembly and HAase-mediated drug release and the interaction between ATP and AMCD. Reproduced with permission from ref 58. Copyright 2021 Royal Society of Chemistry. (b) Schematic illustration of supramolecular magnetic assemblies based on nickel nanoparticle-modified graphene oxide (GONiCD) and HAMitP for alternating magnetic field (AMF)-driven drug release. Reproduced with permission from ref 35. Copyright 2020 Wiley-VCH.

enhance cell permeability and accumulation in tumors, which has extensive application value in biomedical research.

This Account mainly overviews the research progress of our group and other groups in HA-based macrocyclic supramolecular assemblies and their biological applications (Scheme 1), including (i) HA modified by guests, such as pyridinium, adamantane, and cyclohexyl-containing peptides, which exhibit strong binding affinity to CB[*n*]s and *β*-CD; and (ii) CD or CB[*n*] macrocycle-modified HA and its assembly with various guests for multi-stimuli-responsive drug delivery and release, such as the *β*-CD grafted on HA to encapsulate thiol-responsive disulfide-containing adamantane derivatives, redox-type ferrocene derivatives, photostimuli-responsive azobenzene derivatives, and peptide-modified magnetic nanoparticles. Additionally, the research includes permethyl-*β*-cyclodextrin grafted on an HA binding porphyrin/drug conjugate for combined chemotherapy and photodynamic therapy; *in situ* hydrogel formation of CB[6]-modified HA with polyamine derivatives for 3D cell engineering; CB[7]-modified HA with adamantine-modified triphenylphosphine for induced mitochondrial aggregation and fusion; and (iii) direct assembly between unmodified HA and host−guest complexes through multiple hydrogen bonding and electrostatic interactions, such as *γ*-CD encapsulating cationic surfactants as well as CB[7] and CB[8] host−guest complexes with pyridinium derivatives. Finally, we summarize these studies and discuss future development of HA-based macrocyclic supramolecular assemblies in the field of supramolecular diagnosis and treatment.

2. HA-BASED MACROCYCLIC SUPRAMOLECULAR ASSEMBLY

2.1. Supramolecular Assembly Based on Guest-Modified HA

Structurally, HA contains glucuronic acid, carboxylic acid, hydroxyl, and acetylamino groups. Most commonly, carboxylic acid can be modified by esterification and amidation. Therefore, many functional guests, such as luminophores, adamantine, and peptides, are covalently modified to HA. These guests combine with supramolecular macrocycles to form stable host−guest complexes, which not only realize the targeted imaging of cancer cells but also induce organelle aggregation and significantly improve the anticancer effect of drugs.

Regarding bioimaging, purely organic room temperature phosphorescence (RTP) has great potential due to the long emission lifetime, large Stokes shift, high reliability, and so on.[56,57] However, the luminescence of RTP is easily quenched in aqueous systems, which is not conducive to bioimaging. To overcome this shortcoming, our group constructed a water-soluble RTP supramolecular polymer for mitochondria-targeted imaging of tumor cells based on HA-grafted 4-(4-bromophenyl)pyridin-1-ium bromide (HA−BrBP) and CB[8] (Figure 1a).[2] With the aid of the host−guest interaction between the BrBP monomer and CB[8], the formed stable 1:2 complex of CB[8]/BrBP exhibited phosphorescence emission with a lifetime of 1.54 ms and a quantum yield of 2.79%. When

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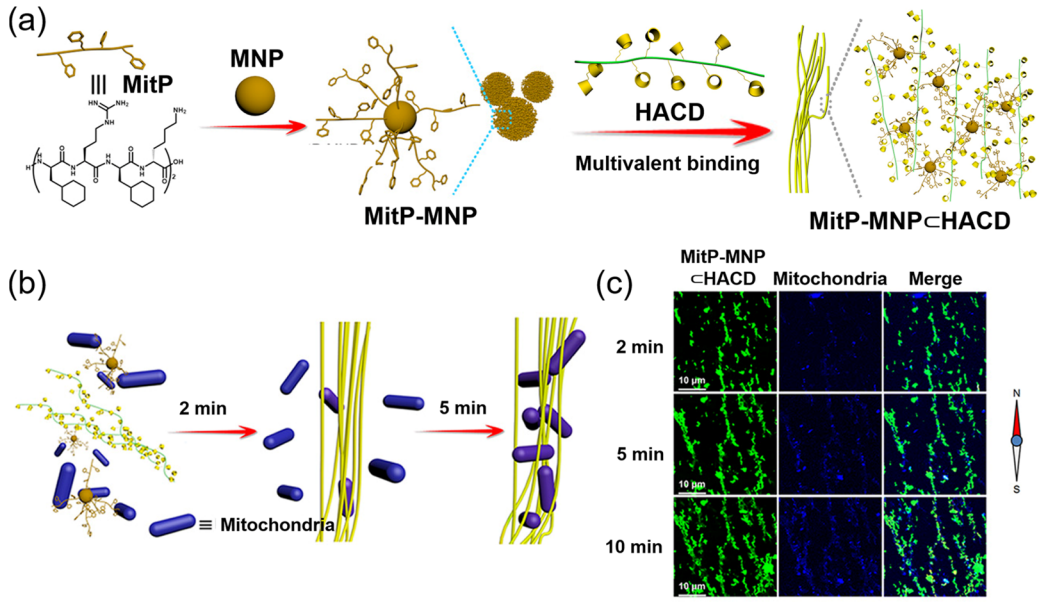

Figure 3. (a) Schematic illustration of the construction of iron oxide magnetic nanofibers MitP-MNP⊂HACD. Reproduced with permission from ref 1. Copyright 2018 The Authors. (b) Schematic illustration of mitochondrial aggregation along the geomagnetic field around MitP-MNP⊂HACD nanofibers. Reproduced with permission from ref 1. Copyright 2018 The Authors. (c) Cell imaging of mitochondria aggregation in the presence of MitP-MNP⊂HACD. Reproduced with permission from ref 1. Copyright 2018 The Authors.

the BrBP monomer was covalently conjugated on HA, the lifetime and quantum yield of CB[8]/HA−BrBP increased to 4.33 ms and 7.58%, respectively. The significant improvement in lifetime and quantum yield is attributed to the double-confinement effect of both host−guest interactions and multiple hydrogen bonding interactions of HA chains, which immobilizes the phosphor and inhibit its nonradiative transition, promotes intersystem crossing from the singlet to triplet state, and prevents triplet excitons from being quenched by oxygen. Based on this CB[8] host−guest interaction for the induction of HA aggregation, we expanded the system to induce *in situ* mitochondrial aggregation for drug-resistant tumor therapy (Figure 1b).[4] Mitochondrial-targeting peptide (MitP) and 4-bromophenylpyridine (BP) are coattached on the HA polymer (HABMitP). Taking advantage of the tumor-targeting ability of HA and the mitochondria-targeting ability of MitP, HABMitP can be specifically taken up by mitochondria in tumor cells, and further addition of CB[8] can induce significant aggregation of mitochondria due to the formation of a 1:2 host−guest complex between CB[8] and BP, which is accompanied by self-reported green phosphorescence (Figure 1c). In cisplatin-resistant MCF-7 tumor cells, the assembly of CB[8] and HABMitP induces mitochondrial aggregation and significantly enhances the antitumor efficiency in the presence of cisplatin. The physical interaction between the mitophagic machine and cisplatin-damaged mitochondria is impaired due to the aggregation of mitochondria, which inevitably hinders the timely eradication of these mitochondria, leading to an increase in the proportion of apoptotic cells from 43 to 96% and completely inhibition of tumor growth *in vivo* (Figure 1d,e). This kind of CB[8]-based host−guest strategy provides a feasible method for the treatment of drug-resistant cancers and biological phosphorescence imaging.

When adamantane (ADA) or cyclohexyl-containing peptide is modified on HA, it can be efficiently encapsulated by β-CD with strong binding affinity to give a large association constant and is beneficial to construct multifunctional supramolecular assemblies. For example, ADA-modified HA (HA−ADA) can form supramolecular assemblies with amphiphilic β-CD to deliver and release the anticancer drug chlorambucil (Cbl) and capture adenosine triphosphate (ATP) (Figure 2a).[58] β-CD modified by seven hexylimidazolium units (AMCD) was selected as the macrocyclic host, and the AMCD can wrap HA−ADA to form an assembly and then load Cbl in the hydrophobic layer. After Cbl@HAAD−AMCD was taken up by tumor cells, the assembly could rapidly release Cbl in the presence of hyaluronidase (HAase). Utilizing the β-CD cavity and multiple imidazolium cationic groups, AMCD displayed a strong binding capacity for ATP to form a stable 1:1 complex, which significantly inhibited ATP hydrolysis and reduced the multidrug resistance of cancer cells, thereby improving the efficacy of chemotherapy. On the other hand, mitochondrial-targeting peptide-modified HA (HAMitP) was used to assemble nickel nanoparticle-modified graphene oxide with covalently grafted β-CD (GONiCD) (Figure 2b).[35] Taking advantage of the β-CD cavity to encapsulate the cyclohexyl group on MitP, GONiCD and HAMitP enabled rapid assembly during doxorubicin (Dox) loading and significantly improved the drug loading capacity. The presence of magnetic nickel nanocomposites can generate heating energy under the stimulation of an alternating magnetic field (AMF), causing the thermally responsive capping to detach from the nanocomposites and subsequently release the drug. Because of the overexpressed HA receptors, the Dox-loaded assemblies can target tumor mitochondria and cause serious damage to mitochondria and nuclei, thereby inducing apoptosis of tumor cells. When the positively charged pyridinium was modified on HA, the pyridinium unit can interact with anionic amphiphilic calixarenes to form drug-loaded assemblies through hydrophobic and electrostatic interactions, which were then taken up by cancer cells via receptor-mediated endocytosis, displaying high cancer cell-targeting and potent anticancer activity.[33] According to the above research, the assembly of guest-modified HA with different macrocycles can not only endow

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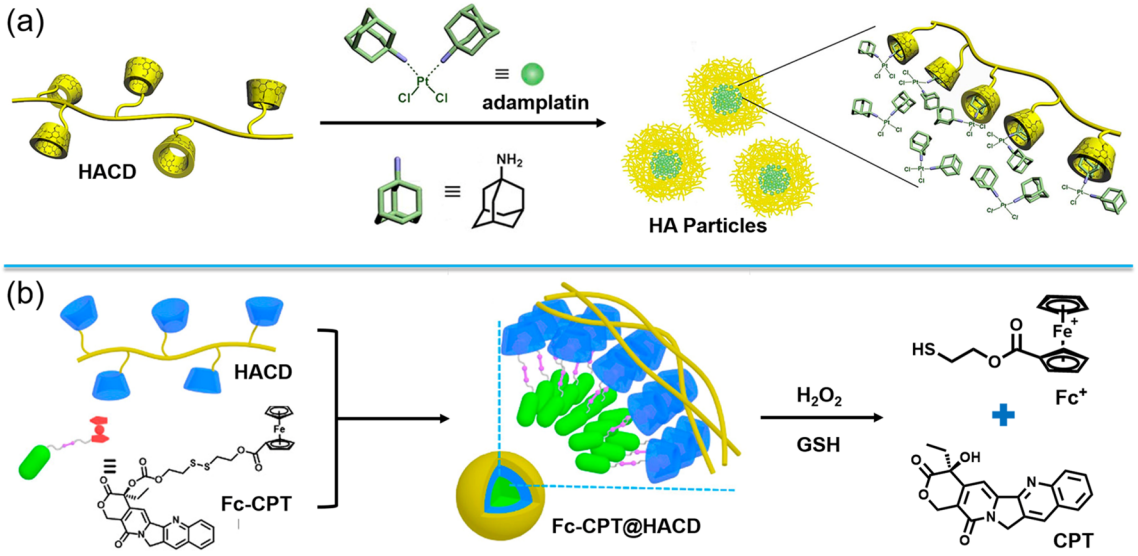

Figure 4. (a) Schematic illustration of HA particles based on HACD and the adamplatin prodrug. Reproduced with permission from ref 68. Copyright 2013, American Chemical Society. (b) Schematic illustration of the supramolecular prodrug assemblies based on ferrocene-modified camptothecin (Fc−CPT) and HACD. Reproduced with permission from ref 69. Copyright 2020, American Chemical Society.

the assemblies with cancer cell targeting but also effectively enhance luminescence efficiency and successfully be applied to synergistic therapy.

2.2. Supramolecular Assembly Based on Macrocycle-Modified HA

Compared with guest-modified HA, macrocyclic-modified HA can directly encapsulate drugs or different kinds of guest molecule derivatives, which is more extensive in constructing multifunctional supramolecular assemblies. The macrocycle encapsulating guests, such as thiol-responsive disulfide-containing adamantine derivatives, redox-type ferrocene derivatives, photostimuli-responsive azobenzene derivatives, and peptide-modified magnetic nanoparticles, provide intelligent functional groups through a strong binding affinity and can be specifically wrapped by the β-CD cavity grafted on HA for drug delivery, bioimaging, and cancer therapy. Different from the permethyl-β-cyclodextrin and cucurbit[n]urils, the parent β-CD possessing multiple hydroxyl groups has strong binding affinity to give a large association constant for size-matched negatively charged guest molecules through hydrophobic and hydrogen bonding interactions. Permethyl-β-cyclodextrin has methoxy groups on its primary and secondary sides and can strongly interact with porphyrin derivatives based on van der Waals interactions.[59,60] Cucurbit[n]urils containing carbonyl groups on their ports can not only encapsulate nonpolar molecules but also bind cationic guests via hydrophobic and ion−dipole interactions. Therefore, these kinds of macrocycle-modified HA have widespread applications in combined chemotherapy and photodynamic therapy, *in situ* hydrogel formation, and induced mitochondrial aggregation and fusion.

For advanced therapy, β-CD-modified HA (HACD) can assemble with iron oxide magnetic nanoparticle (MNP)-coated mitochondrion-targeting peptide (MitP) to inhibit tumor invasion and metastasis (Figure 3a).[1] HACD can be used as a good cross-linker because of the strong inclusion complexation between the β-CD cavity and the cyclohexyl group of MitP. The formed MitP-MNP⊂HACD assemblies undergo magnetic-field-controlled directional aggregation and induce mitochondrial dysfunction and intercellular aggregation in weak geomagnetic fields (Figure 3b,c), ultimately inhibiting the invasion and metastasis of tumor cells *in vivo*. A similar strategy can also be used to construct HACD-based supramolecular assemblies with ADA/actin-binding peptide double-modified iron oxide magnetic nanoparticles for accurately regulating cell polarization[61] and efficient cancer therapy[62] under the action of an alternating magnetic field.

In order to improve the water solubility and biocompatibility of drugs, such as paclitaxel, cisplatin, and camptothecin (CPT), and to reduce drug toxicity and side effects, HACD can directly encapsulate the drugs by using cavities. Auzély-Velty and co-workers used HACD to encapsulate paclitaxel via host−guest interactions and then constructed biocompatible hollow capsules for breast cancer treatment.[63] Because the paclitaxel drug is encapsulated, its efficacy is significantly enhanced, and it is continuously released from the capsule in the presence of HAase, thereby effectively killing breast cancer cells. To achieve highly efficient drug delivery and prolong drug delivery of protein therapeutics,[64,65] some anticancer drugs are modified with adamantyl groups.[66,67] Based on the strong binding affinity of adamantane and β-CD, the obtained drug−adamantane conjugates can be specifically complexed with HACD to target cancer cells and then release drugs in response to multiple stimuli. Therefore, we synthesized four HACDs for adamplatin prodrug delivery, in which the degrees of β-CD substitution were 5.6, 11.5, 16, and 17 (Figure 4a).[68] HACD-17, which exhibits high degrees of substitution, resulted in the highest drug loading performance and a narrow distribution with a hydrodynamic diameter of ca. 180 nm. When nanoparticles are taken up by cancer cells, the encapsulated adamplatin prodrug can be degraded by overexpressed HAase to release the drug in tumor tissue, exhibiting similar anticancer activity to that of cisplatin, but with fewer side effects. Under physiological conditions, redox-responsive drug release can further enhance the targeted therapeutic effect of drugs. To precisely program the release of drug molecules, we modified the ferrocene (Fc) group on CPT through a disulfide bond to obtain the prodrug Fc−CPT (Figure 4b).[69]

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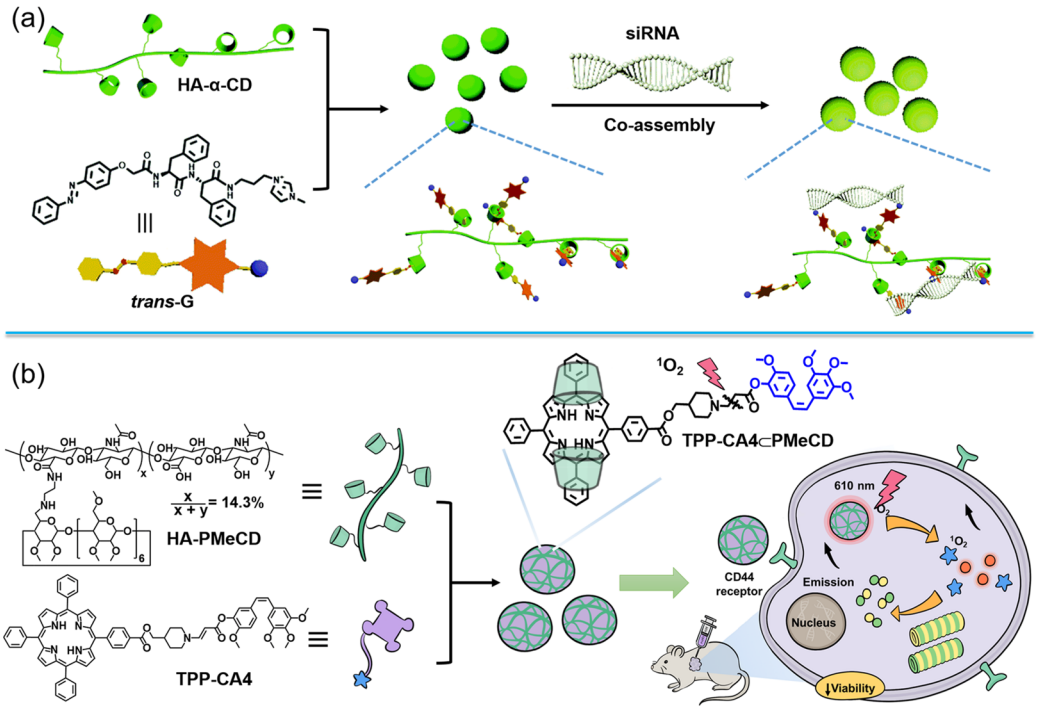

Figure 5. (a) Schematic illustration of the ternary supramolecular nanoassembly for siRNA delivery based on α-CD-modified HA (HA-α-CD) and azobenzene-modified diphenylalanine (*trans*-G). Reproduced with permission from ref 70. Copyright 2020 Royal Society of Chemistry. (b) Schematic illustration of nanosupramolecular assemblies based on permethyl-β-cyclodextrin-modified HA (HA−PMeCD) and porphyrin-modified combretastatin A-4 (TPP−CA4) for self-photocleavable drug release. Reproduced with permission from ref 3. Copyright 2022 American Chemical Society.

Considering the reversible association and dissociation of Fc and β-CD in response to external redox signals, supramolecular assembly can be disassembled. In addition, the disulfide bonds on the disassembled Fc−CPT were more easily cleaved by overexpressed GSH (glutathione), enabling the efficient release of CPT. The above drug delivery systems are only utilized for chemotherapy; however, additional treatments can help overcome the multidrug resistance associated with conventional chemotherapy, resulting in a synergistic effect to improve anticancer outcomes. A much greater effect is obtained through combining two or three of therapeutic agents for tumor combination therapy than through monotherapy, such as photothermal therapy (PTT), photodynamic therapy (PDT), and traditional chemotherapy. Zhao and coworkers reported a reduction-sensitive fluorescent supramolecular prodrug system based on the coassembly of HACD-encapsulated adamantane-linked camptothecin/dye conjugate and IR825, showing an excellent synergistic effect for combinational photothermal−chemotherapy of a tumor.[31]

In supramolecular diagnosis and treatment, photoresponsive drug delivery and release have attracted extensive attention because of their noninvasive and environmentally friendly stimulation. Among the common photoisomeric molecules, azobenzene (Azo) derivatives with water-soluble functional groups are considered ideal candidates for constructing CD-based photoresponsive assemblies, as the *trans* and *cis* Azo group isomers exhibit remarkably different association constants with CDs. By using the host−guest pair of α-CD and Azo, a supramolecular gene nanocarrier was constructed for the highly efficient photocontrolled targeted delivery of siRNA, and this was achieved via the encapsulation of an Azo-modified cationic diphenylalanine guest (*trans*-G) by an α-CD-modified HA (HA-α-CD) (Figure 5a).[70] Because of the strong binding affinity between the Azo group and the α-CD cavity, HA-α-CD and *trans*-G can assemble into nanoparticles with a uniform size of approximately 50 nm. The exposed positively charged imidazole group can interact with siRNA via electrostatic interactions to form larger nanoparticles that exhibit a uniform size of approximately 60 nm. Since the interaction between α-CD and Azo is photosensitive, the capsule can be dissociated under UV irradiation and then release siRNA. This ternary assembly can efficiently deliver siRNA into cancer cells and exhibits excellent gene silencing efficiency under 365 nm light irradiation. Similar to the α-CD and Azo inclusion modes, β-CD can also encapsulate Azo compounds. However, in terms of the binding constant, β-CD is prone to tight encapsulation of large arylazopyrazole derivatives, which contain two methyl groups on the imidazole moiety. Outperforming conventional Azo, arylazopyrazole derivatives exhibit significantly different binding affinities to β-CD during the reversible $E(trans)/Z(cis)$ photoisomerization. Therefore, through the strong host−guest interaction between β-CD and arylazopyrazole unit, HACD-encapsulated upconverting nanoparticles to assemble with spermine-modified arylazopyrazoles have been constructed to achieve highly efficient targeted and controlled gene delivery for cancer therapy.[71]

Compared with the parent β-CD, permethyl-β-cyclodextrin (PMeCD), which is produced by completely replacing the hydroxyl group of β-CD with methoxy group, exhibits good water solubility and biocompatibility. Notably, PMeCD can complex porphyrin derivatives with a strong binding affinity, which not only improves the water solubility of porphyrin derivatives but also prevents the quenching caused by

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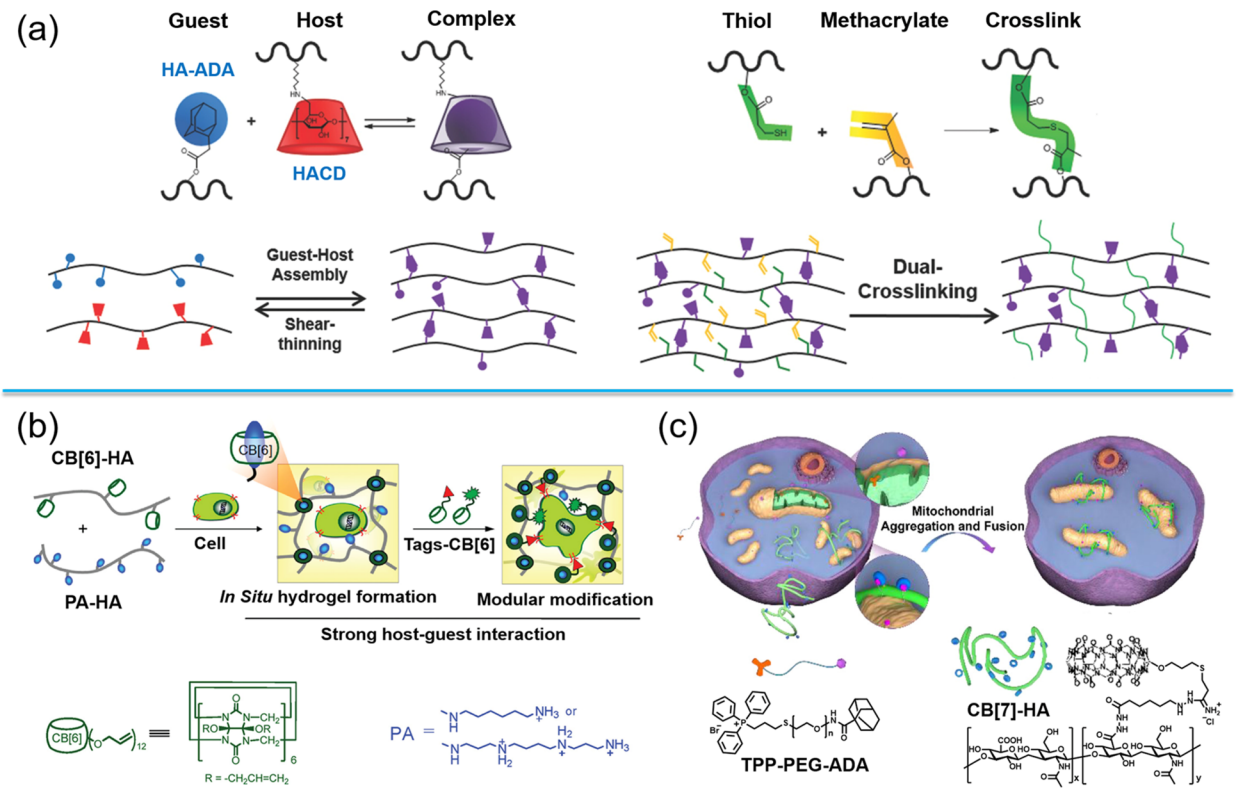

Figure 6. (a) Schematic illustration of HACD/HA−ADA host−guest hydrogel and dual-cross-linking hydrogel on account of both β-CD/ADA interaction and thiol-methacrylate Michael addition. Reproduced with permission from ref 19. Copyright 2014 Wiley-VCH. (b) Schematic illustration of *in situ* hydrogel formation based on CB[6]−HA and polyamine-modified HA (PA−HA). Reproduced with permission from ref 32. Copyright 2012 American Chemical Society. (c) Schematic illustration of supramolecular mitochondrial aggregation/fusion based on TPP−PEG−ADA and CB[7]−HA. Reproduced with permission from ref 77. Copyright 2020 American Chemical Society.

porphyrin self-stacking, thereby improving the fluorescence intensity and the production efficiency of $^1O_2$. Therefore, PMeCD-modified HA was used to encapsulate porphyrin-modified prodrugs to boost self-cleaving drug release (modification degree of PMeCD: 14.3%) (Figure 5b).[3] The porphyrin derivative and microtubule-targeted drug combretastatin A-4 (CA4) are linked by a singlet oxygen ($^1O_2$)-cleavable aminoacrylate group (TPP−CA4), which can assemble with PMeCD to form a 1:2 complex through host−guest interactions. Once the porphyrin moiety is encapsulated in the PMeCD cavity, the production efficiency of $^1O_2$ can be significantly increased by a factor of 60 under illumination at 660 nm and then accelerate the self-photocleavage process, causing the rapid and complete release of CA4. Thus, binary TPP−CA4⊂HA−PMeCD assembly can severely disrupt the microtubule scaffold and effectively inhibit tumor growth by combination therapy. In addition, we also used a disulfide-linked PMeCD−camptothecin prodrug to bind the adamantane-modified porphyrin photosensitizer.[72] The exposed adamantane can further assemble with triphenylphosphine-modified HACD to form stimuli-responsive nanoparticles, realizing chemo-photodynamic synergistic anticancer therapy.

In contrast to the supramolecular assemblies formed by macrocyclic host-modified HA single-chain polymers or guest-modified HA single-chain polymers, macrocyclic host-modified HA polymers can also assemble with guest-modified HA polymers through multivalent interactions,[73] which has great potential in hydrogels and 3D cell engineering. For example, Burdick and co-workers constructed injectable supramolecular hydrogels based on the strong interaction of β-CD and ADA construction units between HACD and HA−ADA for shear-thinning injection and *in vivo* targeted retention. Meanwhile, they constructed secondary covalently cross-linked supramolecular hydrogels via a Michael addition by thiolated HA−ADA and methacrylated HACD to improve the stability of the hydrogel network (Figure 6a).[19] It is noted that multivalent assemblies have also been used in polymer−particle systems that were applied in the development of barriers to surgical adhesion and local drug delivery from granular hydrogels.[74−76] Burdick and co-workers constructed injectable granular hydrogels based on dithiol cross-linked adamantane and norbornene-modified HA microgels and HACD, which can be used for various biomedical applications.[75] Kim and co-workers reported that CB[6]-modified HA (CB[6]−HA) complexation with polyamine-modified HA (PA−HA) can form supramolecular hydrogels *in situ* by utilizing high selectivity and strong binding of CB[6] and polyamines (Figure 6b).[32] Meanwhile, the free PA in CB[6]/PA−HA hydrogel can further interact with functional tag−CB[6] for fluorescence bioimaging. On the other hand, Wang and co-workers proposed a host−guest binding method to induce mitochondrial aggregation and fusion based on triphenylphosphonium/adamantane double-labeled polyethylene glycol (TPP−PEG−ADA) and CB[7]-grafted HA (CB[7]−HA) (Figure 6c).[77] TPP−PEG−ADA can target intracellular mitochondria due to the presence of TPP, in which the ADA moiety is exposed on the surface of mitochondria. By using the strong CB[7]−ADA host−guest interaction, CB[7]−HA can cross-link multiple mitochondria

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Acc. Chem. Res. 2022, 55, 3417−3429

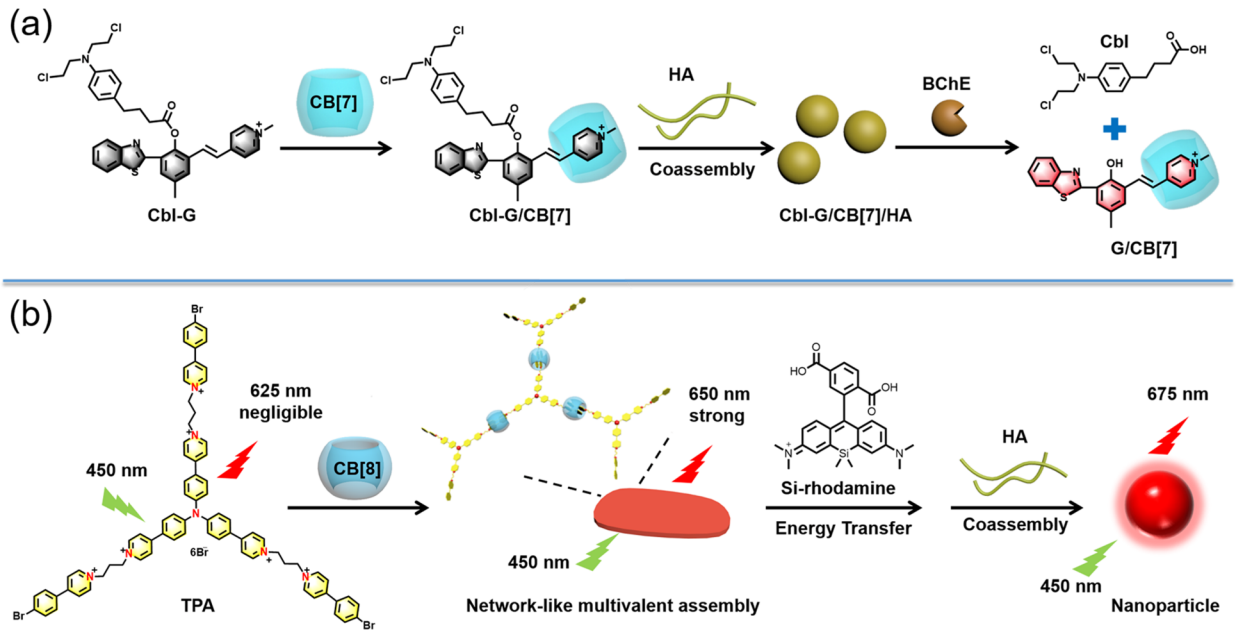

Figure 7. (a) Schematic illustration of the butyrylcholinesterase (BChE)-responsive supramolecular prodrugs for self-reported Cbl release based on CB[7] complexing Cbl-modified dye (Cbl-G) and HA. Reproduced with permission from ref 79. Copyright 2021 Wiley-VCH. (b) Schematic illustration of a multivalent supramolecular energy transfer platform based on CB[8] complexing TPA, Si−rhodamine, and HA. Reproduced with permission from ref 30. Copyright 2022 American Chemical Society.

together, achieving efficient mitochondrial assembly/aggregation and subsequent fusion. From the above work, we can see that the assembly of macrocycle-modified HA with different kinds of guest derivatives has been widely applied in targeted drug delivery, cell imaging, and supramolecular hydrogels.

2.3. Direct Assembly between HA and Host−Guest Complexes

A lot of efforts have been contributed to construct supramolecular assemblies based on guest-modified HA and macrocycle-modified HA by strong host−guest interactions and displaying their inherent unique biological applications. However, the HA itself can also directly assemble with macrocyclic host−guest complexes through multiple hydrogen bonding and electrostatic interactions because of the multiple hydroxyl, carboxyl, and acetamido groups, giving a third efficient assembly method. This assembly approach is mainly easier and more convenient, and the formed supramolecular assemblies can load with different kinds of functional materials, which is important for targeted imaging and drug release. For example, Fenyvesi and co-workers reported a drug delivery platform based on γ-CD encapsulating cationic surfactants with HA through electrostatic interactions, which can be used for controlled release of drugs or proteins.[78] For self-reported anticancer prodrug delivery systems, CB[7] can complex the positively charged pyridinium unit and then coassemble with HA for responsive drug release. Typically, ester bonds are often used as butyrylcholinesterase (BChE) reaction sites, which can be used to link near-infrared (NIR) dye and chlorambucil (Cbl-G) (Figure 7a).[79] Cbl-G assembles with CB[7] to form a stable 1:1 complex and then further assembles with HA to form secondary assemblies through electrostatic interactions and hydrogen bonding. The ester bond in Cbl-G can be efficiently cleaved by BChE, releasing the drug Cbl and the G/CB[7] complex with NIR emission. Due to the presence of CB[7], the G/CB[7] displayed NIR fluorescence emission that was obviously enhanced compared to that of free G. These BChE-responsive secondary assemblies can be easily taken up by cancer cells and not only display good inhibition in malignant cells, in which the side effects are much lower in normal cells, but also achieve *in situ* monitoring of drug delivery.

Through the coassembly of HA, different dyes can be added in multilevel supramolecular assemblies to construct a fluorescence energy transfer platform and applied to NIR targeted cell imaging. This supramolecular assembly platform can be achieved through multivalent assembly of a three-armed 4-(4-bromophenyl)-pyridine-modified triphenylamine (TPA), CB[8], Si−rhodamine, and HA (Figure 7b).[30] TPA can be assembled with CB[8] in a 2:3 (TPA:CB[8]) complexation stoichiometry, and the formed two-dimensional network-like supramolecular aggregates exhibit enhanced red fluorescence emission at 650 nm. Subsequently, Si−rhodamine was added as an energy acceptor via electrostatic interactions, and the energy transfer process was realized through an intermolecular energy transfer pathway with emission wavelength red-shifted to 675 nm. Further coassembly with HA turned this network-like aggregate into nanoparticles, exhibiting further enhanced fluorescence emission, which was stronger than that of the assembly without CB[8]. Taking advantage of the targeting ability of HA, this multivalent supramolecular assembly has been successfully used for lysosomal-targeted imaging in cancer cells.

3. CONCLUSION AND OUTLOOK

In this Account, we systematically summarized the recent research progress on HA-based macrocyclic supramolecular assemblies, mainly including the following assembly strategies: (a) guest-modified HA; (b) host-modified HA; and (c) direct assembly of macrocyclic host−guest complexes with HA. The first strategy mainly utilizes the carboxyl groups to synthesize guest-modified HA through amidation reaction. The functional groups of guest-modified HA can be encapsulated by parent

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macrocycles or macrocycle derivatives to form supramolecular assemblies, which can not only realize targeted fluorescence and phosphorescence bioimaging but also encapsulate drugs for synergistic anticancer treatment. The second strategy utilizes the knowledge that host-modified HA, especially CDs and CB[*n*]s, which have a higher encapsulation ability than that of guest-modified HA because the CDs and CB[*n*]s possess hydrophobic cavity for size-fitted drugs with strong binding affinity, can encapsulate various stimuli-responsive guests to construct multifunctional supramolecular assemblies. The third strategy is to use the multiple hydroxyl, carboxyl, and acetamido groups of HA to directly assemble with macrocyclic host−guest complexes through hydrogen bonding and electrostatic interactions. In this assembly process, the macrocycles first encapsulate and isolate the guest, which effectively prevents the aggregation-caused quenching of luminescent molecules, thereby improving their bioimaging resolution and PDT effect. For the direct assembly of HA with host−guest complexes, the introduction of electrostatic interactions with HA was beneficial to the construction of assembly and stability improvement; various drugs or prodrugs are first encapsulated in the macrocycles' cavity and then can be loaded in the assemblies for drug delivery. The different drugs and targeted agents can be coloaded in the HA-based assemblies for synergistic therapy and bioimaging. Obviously, these three synthetic approaches mainly rely on strong binding affinity to construct HA-based assemblies. For the enhancement of application of assemblies, other stimulus-responsive functional guests and targeted biomolecules can be modified onto HA. In the HA modification, the degree of substitution should be considered, because excessive substitution at the carboxyl site will reduce the targeting ability of HA. According to the therapeutic effects of HA on angiogenesis and macrophage polarization, HA-based macrocyclic host−guest assemblies will broaden their biological applications. For better theranostic outcomes, the diversity of HA-derived assemblies still needs to be strengthened. Other kinds of macrocyclic hosts such as pillararenes, calixarenes, and biphen[*n*]arenes are appealing for modifying HA. By using the host−guest interaction, the modified macrocycles interacting with biomacromolecular surface groups can facilitate the allosteric effects of disease-related active sites. In addition, specific protein aggregation and organelle aggregation can also be achieved, which will help to enhance the anticancer effect of drugs.

From the above review, we can see that HA-based macrocyclic supramolecular assemblies are a rapidly developed research field in supramolecular diagnosis and treatment, and there are many challenges. As an excellent carrier, HA can assemble a variety of drugs, photosensitizers, or enzymes into a nanosupramolecular assembly, which can enter cancer cells through receptor-mediated endocytosis, realizing the purpose of precision diagnosis and treatment. This can help or be used to treat specific ailments such as cancer and diabetes. In terms of molecular recognition and bioimaging, the construction of nanosupramolecular assemblies with NIR emission and two- or three-photon excitation for deep tissue and *in vivo* imaging is still a future direction. Another interesting and worthwhile approach is to coattach two or more functional groups on HA, such as organelle targeting groups, imaging agents, drugs, and photosensitizers, among others, to construct multifunctional supramolecular assemblies for synergistic multimodal therapy. The attachment method can be modified by covalent chemical bond or noncovalent host−guest interaction,[80] such as the CB[6]−HA that attached by spermidine-modified imaging, drug, and targeting agents.[20] It can be seen that the HA-based supramolecular assemblies will have broad applications in the fields of drug delivery and bioimaging, inducing aggregation of microfilaments, microtubules, enzyme proteins, and mitochondria as well as reducing the multidrug resistance, *in situ* hydrogel formation for soft materials, and so on, which will contribute to the rapid development of chemistry, materials, biology, and other related disciplines. We hope that this Account will inspire scientists to create more various supramolecular assemblies and to explore their biological applications.

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Z.L. and W.L. contributed equally to this work. CRediT: **Zhixue Liu** writing-original draft (lead); **Wenjing Lin** writing-original draft (equal); **Yu Liu** supervision (lead).

Notes

The authors declare no competing financial interest.

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Zhixue Liu was born in 1987 in China. He received his PhD degree from Yanbian University in 2017 under the supervision of Prof. Xue Wu. After that, he worked as a lecturer at Jilin Normal University for one year. Since 2018, he has been working as a postdoctoral researcher at Nankai University under the supervision of Prof. Yu Liu. His current research focuses on the construction of supramolecular optical sensors and functional supramolecular assemblies.

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Yu Liu was born in 1954 in Hohhot, Inner Mongolia, China. He graduated from the University of Science and Technology of China in 1977 and received his PhD degree from Himeji Institute of Technology, Japan, in 1991. Then, he moved to Nankai University as a full professor in 1993. His research focuses on molecular recognition and assembly of macrocyclic receptors.

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Acc. Chem. Res. 2022, 55, 3417−3429

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Acc. Chem. Res. 2022, 55, 3417−3429

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