Drug/Gene Delivery Platform Based on Supramolecular Interactions: Hyaluronic Acid and Folic Acid as Targeting Units

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Yang Yang

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52.1 Introduction

In recent years, nanotechnology has developed rapidly in construction of nanoparticles, carbon nanomaterials, vesicles, micelles, hydrogels, etc., for application on drug delivery, gene delivery, cellular imagination, and other biological utilities. For a large number of reported nanoplatform with excellent bio-functions, the author believes that the nanoplatform which had potential in real clinic application should fulfill the following requirements: (a) good aqueous solubility in physiological environments; (b) targeted internalization by receptor-mediated endocytosis to promote the drug/gene delivery efficiency and decrease the side effects; (c) controlled release at targeting site to further enlarge the therapeutic effects; (d) biocompatibility and biodegradability to weaken the immunogenicity and biotoxicity of delivery system and prolong the circulation time in vivo; and (e) simplification in nanoplatform design and fabrication. Therefore, the nanoplatforms constructed by supramolecular interactions could totally meet the abovementioned conditions, where

Y. Yang (✉)
School of Chemical Engineering and Technology, Hebei University of Technology, Tianjin, China
e-mail: yangyang0410@hebut.edu.cn

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supramolecular building blocks were facilely synthesized, and could introduce multiple targeting units and biocompatible units onto the platform conveniently, and the supramolecular hosts (such as β-cyclodextrin) were highly water soluble and could bind with and release drug molecules in a reversible way. In this chapter, we simply review the latest progress on supramolecular nanoplatform employed folic acid (FA) or hyaluronic acid (HA) as targeting units to enhance the specificity toward cancer cells with excellent biocompatibility and biodegradability in recent 5 years, because rapidly growing reported studies along with their theoretical principals are required for fully understanding and exploring the great potential of this approach.

52.2 Folic Acid

Folic acid (FA) is a kind of natural vitamin widely distributed in fruit, vegetables, liver, etc. FA is a necessity for pregnant woman because FA could provide nucleobases during biosynthesis of purine and pyrimidine and then facilitate the cell division in embryonic development. On the other hand, cancer cells are malignant proliferating cells with rapid division speed. Therefore, FA could be especially recognized by over-expressed FA receptor and largely internalized by cancer cells due to their malignant proliferation nature. Before 2010, the investigation upon FA was still limited to the research of its self-assembly behavior and liquid-crystal property improvements. The hydrogen bond interactions between petrin rings of FA would induce the FA derivatives to form planar tetrameric or hexameric supramolecular disks, which could further self-assemble by π-π stacking interactions to generate supramolecular cation channels or supramolecular chiral columns for liquid crystalline applications [1, 2]. Recently, the high affinity between FA and FA receptor on cancer cell surface made FA as an ideal targeting unit for drug/gene delivery.

52.2.1 Folic Acid Used as Targeting Unit on Nanoparticle/Nanoplatform Surface

The high affinity toward folate receptor on the surface of cancer cells made FA always used as targeting units in drug/gene delivery nanoparticles. However, most of these nanoparticles were self-assembled from FA modified amphiphilic polymers, which were composed of hydrophilic PEG linker and hydrophobic polymer main chain [3–5]. The synthetic routes were tedious, and operation process was complicated. Thus, folic acid-based building blocks could be applied to simplify the system and could be introduced onto nanoparticle surface through facile supramolecular interactions.

Yu Liu's group firstly synthesized β-cyclodextrin (β-CD)-modified folic acid (FACD) for targeting drug delivery [6]. As shown in Fig. 1, π-π stacking and supramolecular interactions could integrate graphene oxide (GO), doxorubicin (DOX), adamantanyl porphyrin, and FACD together to produce quaternary supramolecular targeted delivery platform. This platform had high DOX loading amount and good dispersity in aqueous solution and could target transport DOX into HeLa

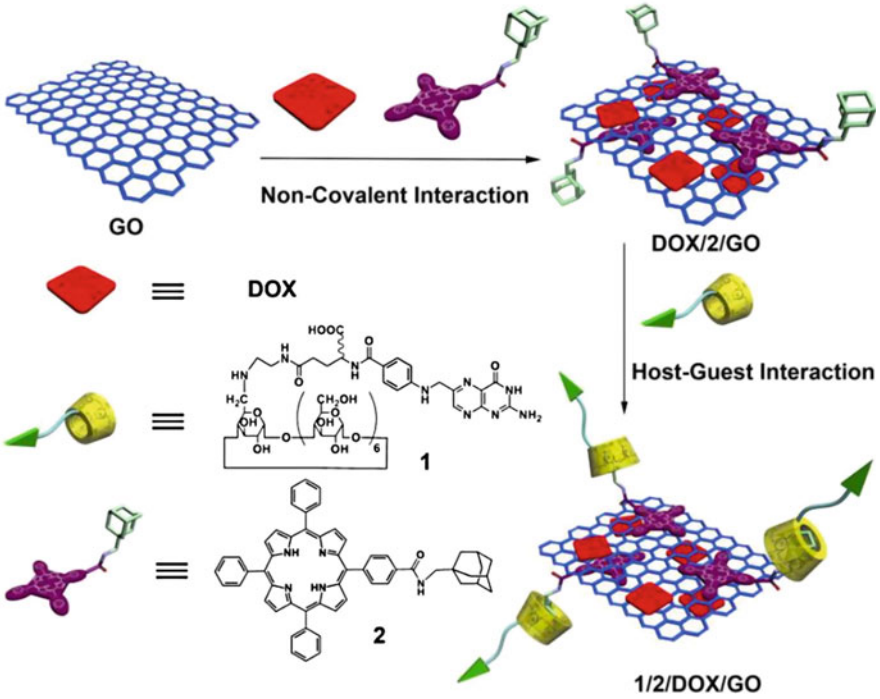

Fig. 1 The construction process of quaternary supramolecular targeted DOX delivery platform. (Copyright 2012, Wiley-VCH Verlag)

cancer cells through folate receptor-mediated endocytosis without imparting serious side effects in vitro and in vivo. The building block strategy in this work might provide important inspiration to the construction of multifunctional supramolecular biomaterials in a facile way.

Similar mechanism was also utilized by Hoon Hyun et al. [7] to construct simple supramolecular complex instead of fabricating complicated nanoparticles. In a typical process, biocompatible polyethylene glycol (PEG) was jointed with FA on one side, and with β-CD on the other side, to obtain CDPF unit. Then adamantane was connected with near-infrared fluorophore ZW800-1 to form ADM-NIRF. The supramolecular interactions between β-CD and adamantane would combine host CDPF and guest ADM-NIRF together as a CDPF-ADM-NIRF complex, which exhibited remarkable tumor-targeting and near-infrared fluorescent imagination toward MCF-7 cancer cells and tissues in vivo (Fig. 2).

Folic acid modified cyclodextrin could be also employed to load drug directly. Jun Li et al. [8] developed multiple (OEI) arms with FA-conjugated γ-CD, whose cavity could bind anticancer drug Paclitaxel (PTX). The positive charged arms of γ-CD-OEI-SS-FA/PTX complex associated with negative charged pDNA form polymer/DNA polyplex nanoparticles to carry PTX and pDNA targetedly into KB cancer cells. Therefore, the simultaneous gene transfection and nto one cancer cell were

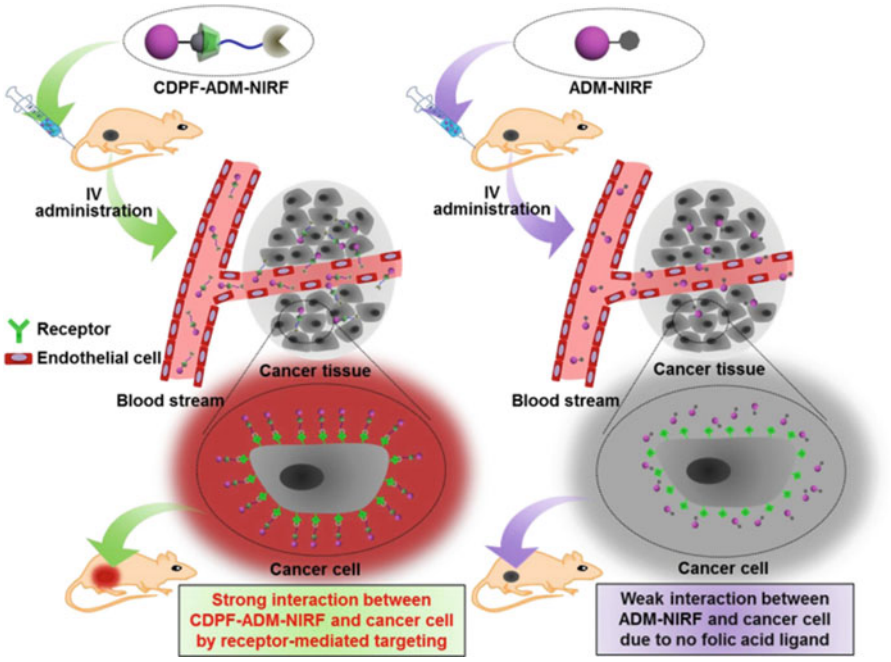

Fig. 2 Active tumor-targeting illustration of CDPF-ADM-NIRF complex and guest ADM-NIRF alone. (Copyright 2018, Elsevier)

realized with high efficiency, which could be considered promising for cancer therapeutic application (Fig. 3).

Yanli Zhao et al. [9] developed a supramolecular self-assembly nanoparticle based on multiple adamantane or β-CD-modified building blocks to introduce various functions into nanoparticles. Firstly, polyacrylates functionalized with adamantane and β-CD (PAA-AD and PAA-CD) were mixed together to self-assemble to form supramolecular nanoparticles through strong host-guest complexation between adamantane and β-CD. Meanwhile, adamantane-modified polyethylene glycol (PEG-AD), adamantane-functionalized folic acid (FA-AD), and adamantane-conjugated fluorescein isothiocyanate (FITC-AD) were also grafted onto the nanoparticles to improve the biocompatibility, targeting capability, and fluorescent imaging ability, respectively. The prepared nanoparticles were proven to be noncytotoxic, and biological experiments in vitro and in vivo showed that after loading doxorubicin (DOX), the DOX-loaded nanoparticles could targetedly recognize and be internalized into cancer cells and tissues through FA receptor-mediated endocytosis without damaging the healthy cells (Fig. 4).

FA-AD could be also used as building blocks in targeted gene delivery nanoparticles. Bo Yang et al. [10] synthesized β-CD-grafted low-molecular-weight branched polyethylenimine (PEI-CD). Due to the supramolecular interactions between adamantane and β-CD, PEG-AD and FA-AD were simultaneously

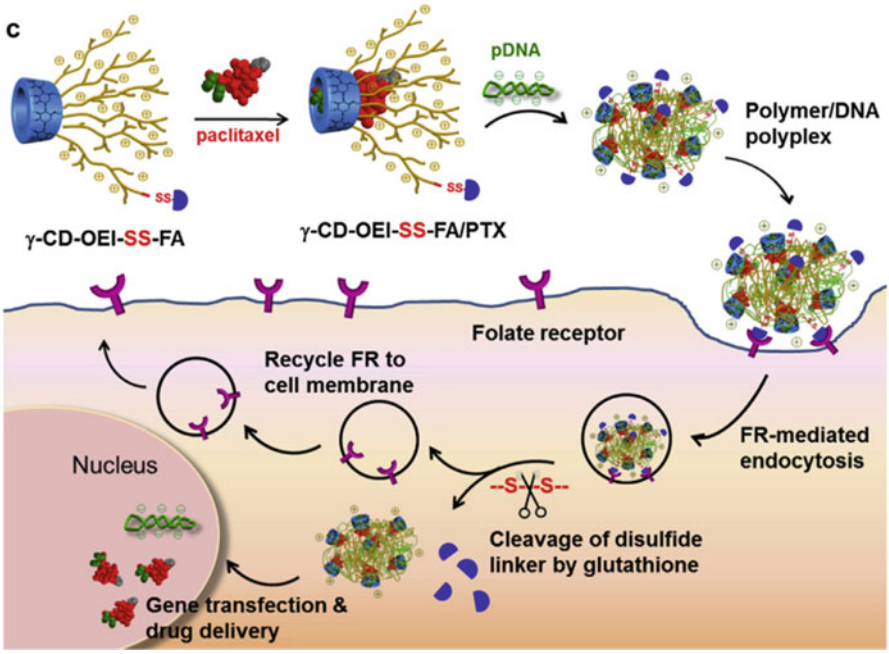

Fig. 3 Illustration of the concept of the drug and gene co-delivery mediated by the polymer/DNA polyplex nanoparticles. (Copyright 2014, Elsevier)

introduced onto PEI-CD aggregation to increase the biocompatibility and targeting efficiency. Then, after association of plasmid DNA (pDNA), "multilayer bricks-mortar" type of nucleic acid delivery vector was obtained. This vector exhibited lower cytotoxicity than branched PEI 25 kDa with maintained transfection efficiency. This work suggested that the gene carrier, based on multivalent host-guest interactions, could be an effective, facile, targeted, and low-toxicity carrier for delivering nucleic acid into target cancer cells (Fig. 5).

After that, Nikhil R. Jana et al. [11] found that native FA could be also introduced onto nanoparticles' surface by simple host-guest interactions. CdSe/ZnS-based quantum dots (QDs) were conjugated with β-CD, which could include FA and riboflavin into cavities to introduce double targeting units onto QDs' surface. Therefore, enhanced targeting effects and cellular fluorescent labeling could be observed in various cancer cells, such as A431 cells and KB cells (Fig. 6).

Salvatore Sortino et al. [12] reported a much simpler strategy to realized targeted porphyrin delivery by organic-inorganic hybrid materials. They encapsulated *meso*-tetrakis(4-carboxyphenyl) porphyrin (TCPP) and FA in situ into pores of mesoporous silica material, and TCPP and FA were compelled to stack alternatively through π-π stacking interactions. After release from silica pore, the FA/TCPP assembly was internalized by KB cancer cells by FA receptor-mediated endocytosis, and the enrichment of TCCP in cancer cells would cause enhanced cell death by photodynamic therapy (PDT) under irradiation of UV light (Fig. 7).

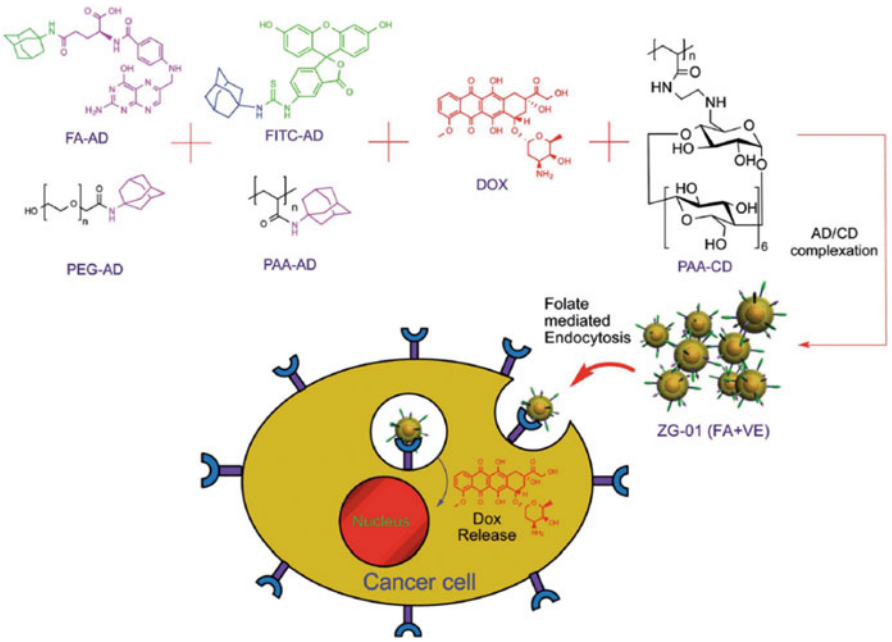

Fig. 4 The construction of supramolecular nanoparticles based on PAA-CD, PAA-AD, PEG-AD, FA-AD, and FITC-AD. (Copyright 2014, The Royal Society of Chemistry)

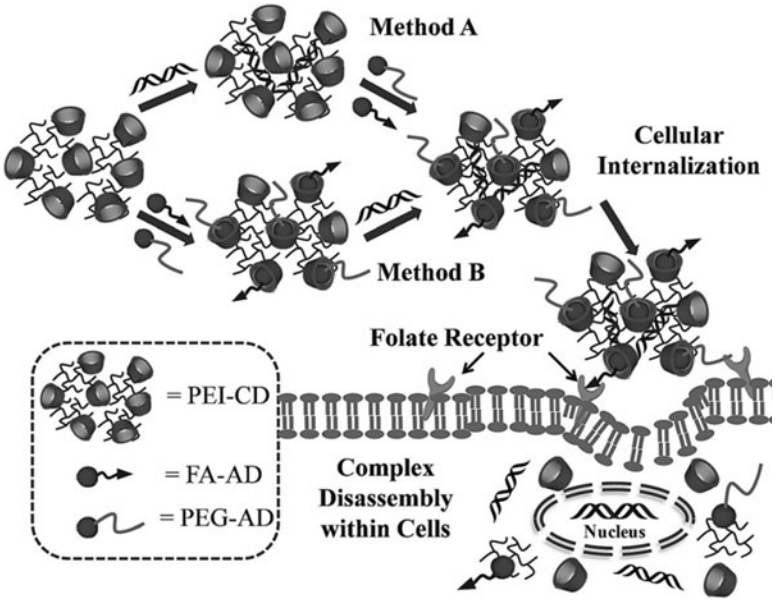

Fig. 5 The construction process of FA-targeted self-assembling gene delivery vector. (Copyright 2015, Wiley-VCH Verlag)

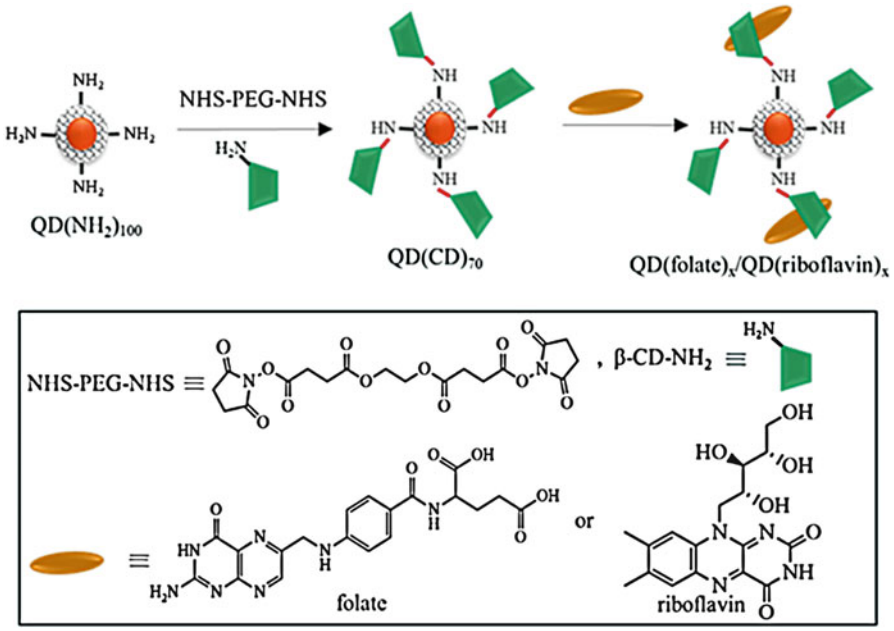

Fig. 6 Synthetic approach to folate/riboflavin-functionalized quantum dots by supramolecular interactions. (Copyright 2017, American Chemical Society)

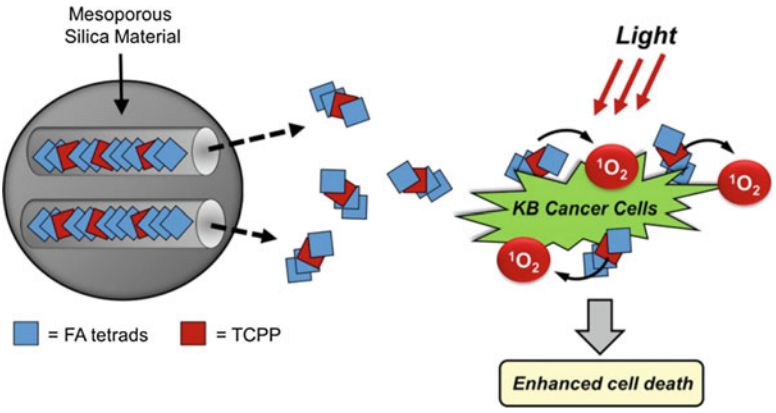

Fig. 7 Illustration of the targeted PDT with FA/TCPP assembly released from the mesoporous silica material. (Copyright 2017, Wiley-VCH Verlag)

Besides abovementioned *β*-CD-based supramolecular interactions, noncovalent interactions of pillararene and charged guests were also taken into account. For instance, Feihe Huang et al. [13] investigated host-guest recognition effects between cationic pillar[6]arene and AMP, ADP, or ATP. The

especially strong affinity between pillar[6]arene and ATP could protect ATP from hydrolysis, which might facilitate to overcome multidrug resistance (MDR). Then a folic acid ended diblock polymer FA-PEG-*b*-PAA was synthesized and complexed with pillar[6]arene to form stable polyion complex (PIC) micelles carrying doxorubicin (DOX) into drug resistant MCF-7/ADR cancer cell in a targeted way. The disassociated pillar[6]arene could bind cellular ATP to block the efflux pump to transport anticancer drugs out of cells by cutting off the energy source, and the therapeutic effects of released DOX could be greatly improved (Fig. 8).

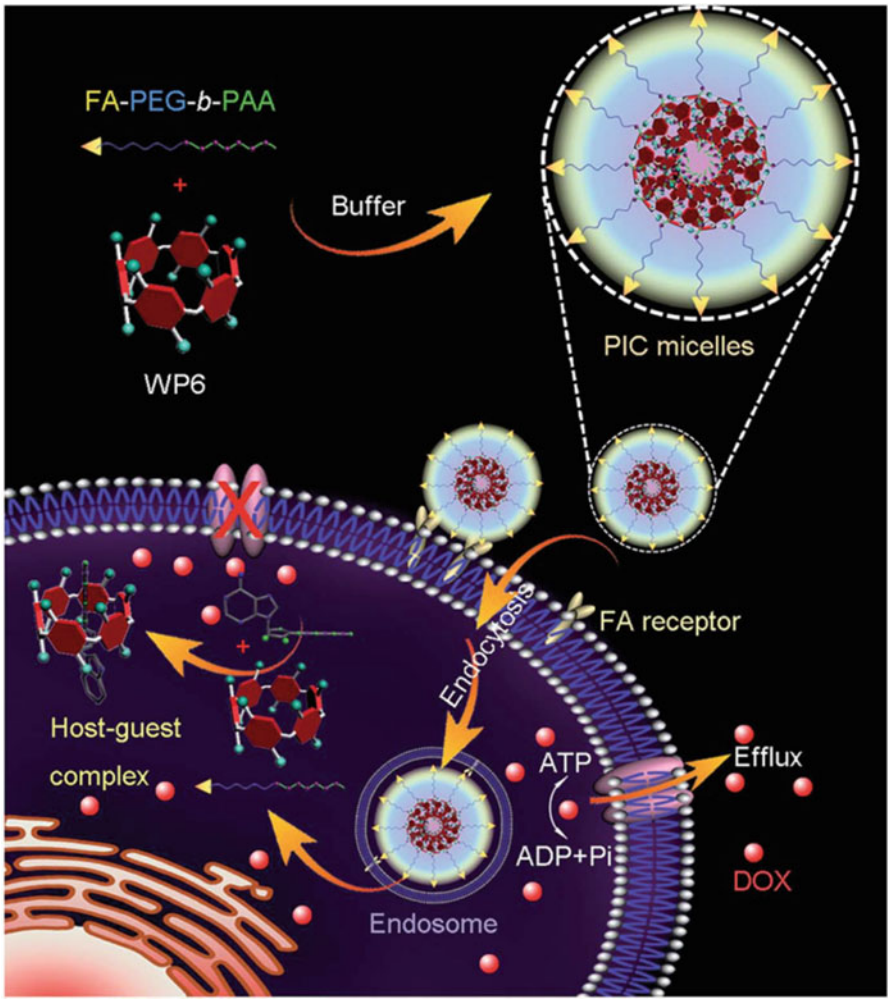

Fig. 8 The targeted delivery process of PIC micelles into drug- resistant cancer cells. (Copyright 2016, The Royal Society of Chemistry)

Ying-Wei Yang et al. [14] constructed polypyrrole@UiO-66 nanohybrids covered by pillar[6]arene-based pseudorotaxanes, and FA-modified polyethyleneimine (PEI) was then introduced onto the nanoparticles' surface through electrostatic interactions. The obtained PUWPFa NPs could load chemotherapeutics 5-fluorouracil in polypyrrole core, which could be released under pH/temperature dual-stimuli response. Together with photothermal conversion capability of polypyrrole core, the chemophotothermal united therapy of PUWPFa NPs toward HeLa cancer cells and tissues in vitro and in vivo could be realized (Fig. 9).

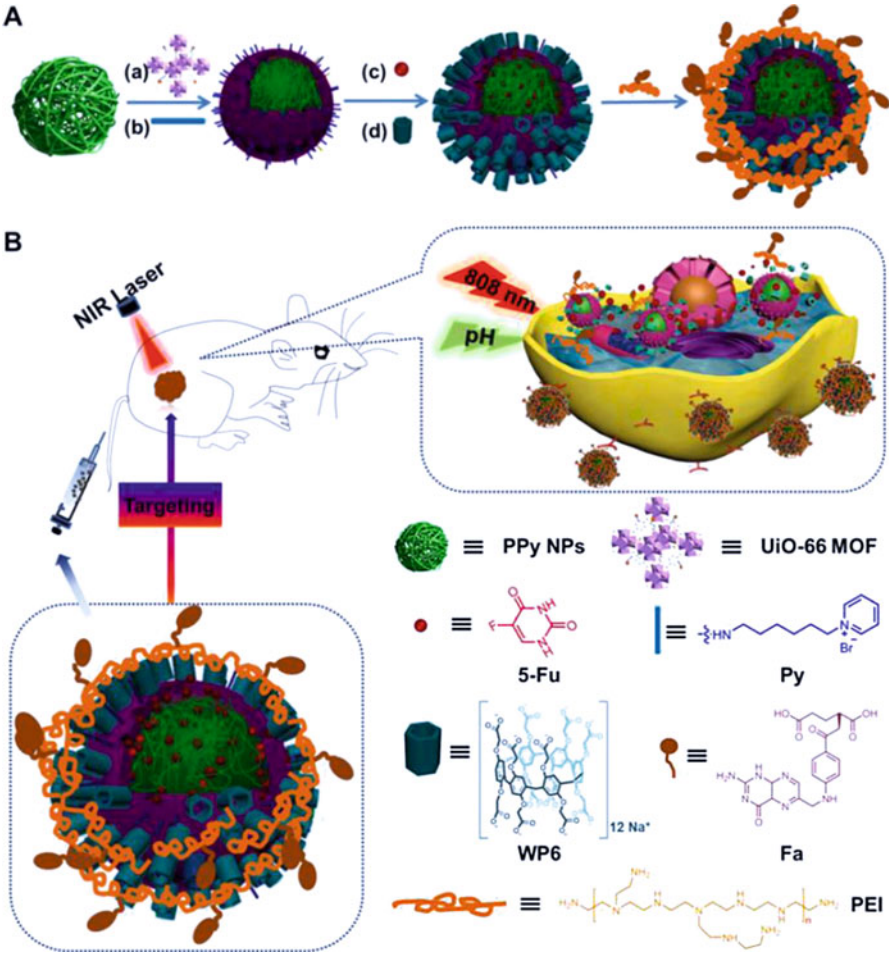

Fig. 9 The illustration of PUWPFa NPs' preparation and chemophotothermal application in mice. (Copyright 2018, American Chemical Society)

52.2.2 Folic Acid Hydrogels

Aiyou Hao et al. [15] and Yun Yan et al. [16], respectively, discovered the novel metallo-folate supramolecular hydrogel in similar preparation strategy by self-assembly of small-molecule crude FA driven by naturally occurring supramolecular interactions. This extraordinary hydrogel was fabricated through a sequence of hierarchical steps. Firstly, petrin rings on folate were tetramerized by hydrogen bonding interactions to form planar tetramers. Then the tetramers were stacked into nanofibers through π-π stacking, and the obtained nanofibers were further cross-linked by zinc ions to form larger-scale fibrils network, which were finally cross-linked to gel water. The supramolecular qualities of hydrogel endowed it with shear-thinning and instant healing ability, and these excellent properties would make the hydrogel injectable and printable into various three-dimensional structures. The prepared hydrogel could be used as an ideal candidate material for chemotherapeutic drug and MRI imaging agent (Gd^{3+}) delivery (Fig. 10).

52.3 Hyaluronic Acid

52.3.1 Hyaluronic Acid-Based Supramolecular Vesicles and Nanoparticles

Hyaluronic acid (HA) is a kind of natural hydrophilic linear polysaccharide composed of *D*-glucuronic acid and *D*-*N*-acetylglucosamine units interlinked with alternating *β*-1 → 4 and *β*-1 → 3 glycosidic bonds, which is widely existed in ocular

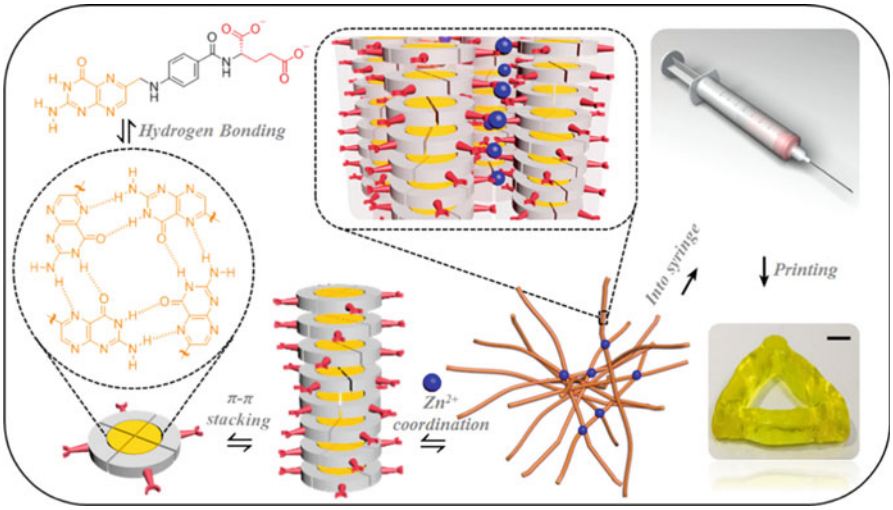

Fig. 10 The construction process of FA-Zn^{2+} hydrogels. (Copyright 2018, American Chemical Society)

vitreous body and intercellular matrix, and worked as natural moisturizing factors. Moreover, HA could also influence the cell proliferation and migration, inflammation, wound repair, cartilage formation, and differentiation. Recent research showed that most of malignant proliferating cells as well as carcinoma cells overexpressed HA receptor on the cytomembrane, such as CD44 and RHAMM receptor, which could strongly bind HA with at least six successive saccharide repeating units. Besides, HA could be metabolized by hyaluronidase in cytoplasm, together with the wide existence of HA in organism, which both decide HA's biocompatibility and biodegradability. The carboxylic group in HA facilitates the facile modification as supramolecular building blocks.

Thus, the biocompatible nature and targeting capability toward CD44 receptor over-expressed on cancer cells would make HA as excellent candidate material in supramolecular vesicles and nanoparticles for drug/gene delivery. The most commonly used approach is introducing hydrophobic part onto the backbone of HA by covalent or noncovalent method, and then the HA derivative becomes amphiphilic and forms vesicles or nanoparticles in aqueous solution. In this portion, recent progress of HA vesicles and nanoparticles based on supramolecular and other noncovalent interactions is emphatically summarized, because HA building blocks including nature HA or HA derivatives from facile chemical way are easily acquired.

52.3.1.1 Nature HA Nanoparticles

Firstly, nature HA was directly employed to construct nanoparticles. Françoise Chuburu et al. [17] reported a relative facile approach to construct chitosan nanoparticles (CS NPs) using modified chitosan and crude hyaluronic acid. As shown in Fig. 11, $mPEG_{2000}$ was grafted onto chitosan with different degree of substitution. Then HA and tripolyphosphate (TPP) were binded with $mPEG_{2000}$-modified chitosan under ionic gelation process to form CS-$mPEG_{2000}$-TPP/HA nanogels.

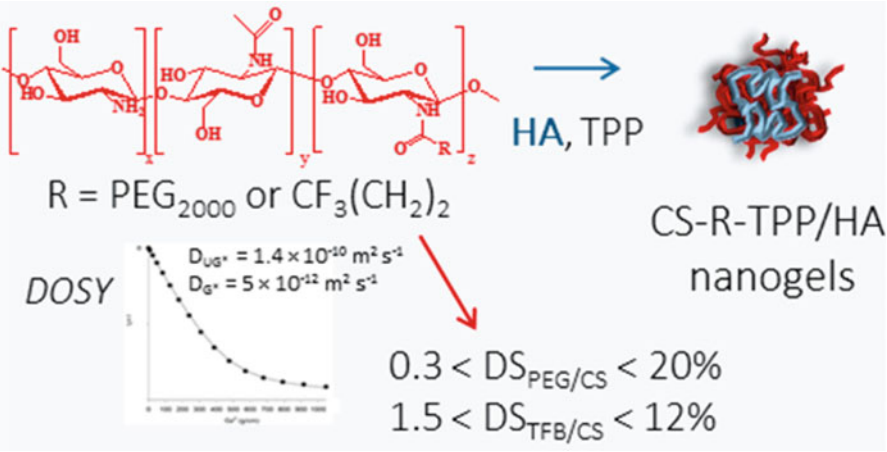

Fig. 11 The construction of CS-$mPEG_{2000}$-TPP/HA nanogels. (Copyright 2017, American Chemical Society)

The $mPEG_{2000}$ composition could not only increase the solubility of the nanogels but also improve the pharmacokinetic and pharmacodynamic properties due to the nonionic hydrophilic character. Therefore, the nanogels exhibited great compatibility and noncytotoxicity toward RAW 264.7 murine macrophages. Together with the targeting capability of HA, the prepared series of CS nanogels might encapsulate probes for targeted MRI.

Ja-Hyoung Ryu et al. [18] synthesized a novel indocyanine dye derivative IR-Pyr with positive charge to solve the poor solubility of PDT sensitizer. Then the positive charged IR-Pyr interacted with negative charged natural HA through electrostatic effect to obtain the supramolecular amphiphiles, which immediately self-assembled to micellar aggregate HA-IR-Pyr. The novel micelle HA-IR-Pyr could recognize CD44 receptor positive and hyaluronidase overexpressed HeLa cells, and the released sensitizer IR-Pyr showed mitochondria-targeting capability to promote the PDT effect. Therefore, the HA-IR-Pyr has confirmed high PDT effect toward cancer cells and tissues in vitro and in vivo without causing serious side effects to normal tissues (Fig. 12).

Besides abovementioned electrostatic interactions, supramolecular interactions could also be employed to fabricate nature HA-based nanoparticles. Eva Fenyvesi et al. [19] reported biodegradable polymer assemblies for electrostatic-driven drug delivery in a facile way. As shown in Fig. 13, the supramolecular matrix was cross-linked by supramolecular interactions between γ-CD and hexadecyl(2-hydroxyethyl)dimethylammonium dihydrogen phosphate (HHDDP) in a 1:2 way and electrostatic interaction between positively charged HHDDP and negatively

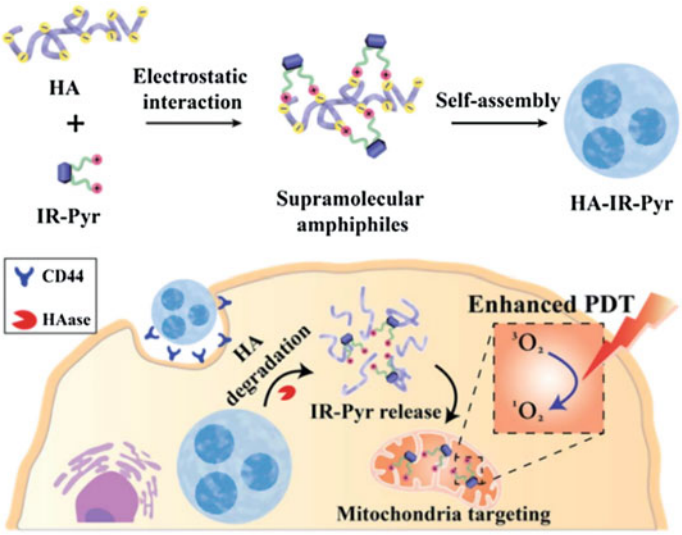

Fig. 12 The HA-IR-Pyr micelle fabrication and cancer cell-/mitochondria-targeting process. (Copyright 2017, The Royal Society of Chemistry)

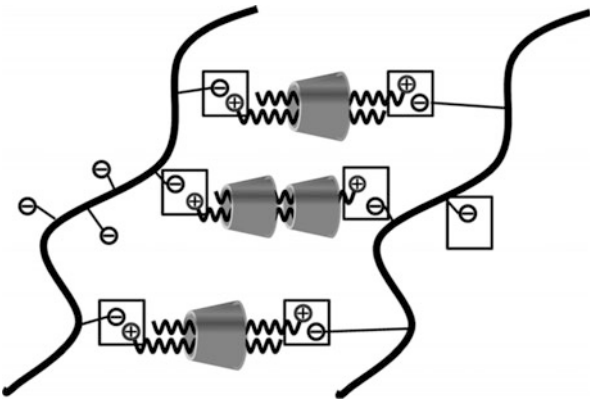

Fig. 13 Hypothetical structure of electrostatically cross-linked HA with the HHDDP/γ-CD inclusion complex. (Copyright 2014, Wiley-VCH Verlag)

charged nature HA. The obtained supramolecular network was biodegradable and could load small-molecular and protein model drugs into the matrix.

52.3.1.2 Covalent HA Nanoparticles

In order to introduce more functional groups into HA and further improve the physicochemical properties of HA, direct functionalization on HA through covalent interactions, such as esterification and amide reaction, is the routine and frequently used method for grafting drugs and imaging probes and other agents onto HA backbones in the early stage of HA derivatives' preparation due to the existence of carboxylic groups on the HA backbone. For example, Oommen P. Oommen et al. [20] covalently modified hydrophobic fluorescein onto HA to obtain amphiphilic HA nanoparticle (HA-NP), which could stabilize anticancer drug doxorubicin (DOX) into nanoparticle by π-π stacking and hydrophobic interactions. The fabricated HA-NP showed CD44 dependent cellular uptake into HCT-116 and MCF-7 cancer cells, while promoted DOX release and cytotoxicity in cancer cells were also observed (Fig. 14).

Hyung Jun Ahn et al. [21] designed a tumor-specific nanoparticle for siRNA delivery, which was composed of cholesterol-bearing hyaluronic acid (HA-Chol) and 2b RNA-binding protein (2b)/siRNA complexes. The amphiphilic nature of HA-Chol would induce the formation of nanoparticle with hydrophilic HA shell and hydrophobic Chol core, which could contain (2b)/siRNA by hydrophobic interactions in contrast to the traditional siRNA binding using electrostatic interactions. The obtained nanoparticle could selectively deliver 2b protein/siRNA complexes to the tumor cells with up-regulated CD44 receptors and suppress the expression of target gene. This well-designed delivery systems could provide encapsulation, protection, and targeted delivery of siRNA and demonstrate the promising potential of the efficient siRNA carriers in the anticancer therapeutic applications (Fig. 15).

On the other hand, Qiaobing Xu et al. [22] developed a novel targeted protein delivery system based on HA and cationic lipid. As shown in Fig. 16, cytotoxic protein ribonuclease (RNase) A was firstly connected onto HA backbone through

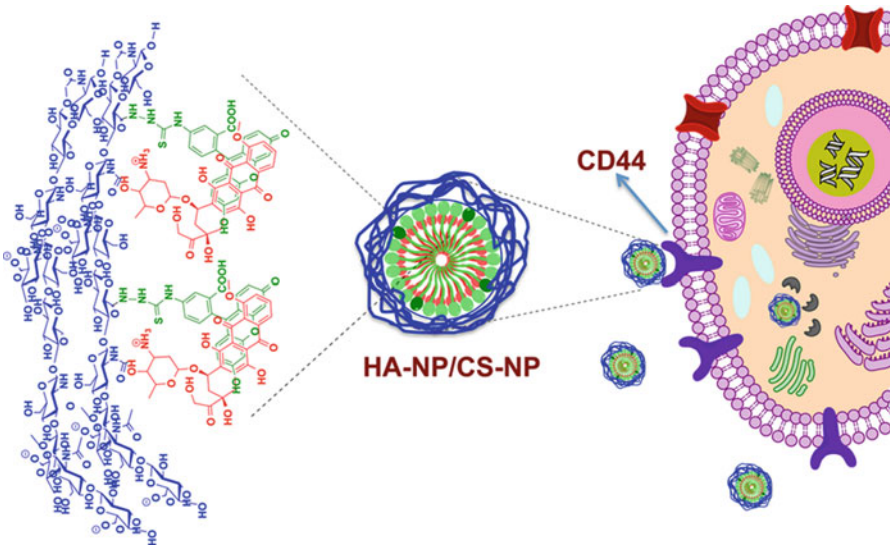

Fig. 14 Cellular uptake of HA-NP into cancer cells through HA-CD44 interaction. (Copyright 2016, American Chemical Society)

amide condensation reaction. Then the prepared RNase A-HA was mixed with cationic lipid to form lipid-like nanoparticles through electrostatic interactions between negative charged RNase A and positive charged cationic lipid. The lipid-like nanoparticles EC16-80/RNase A-HA could enter cancer cells with high CD44 expression and inhibit cancer cell proliferation in a dose-dependent manner.

52.3.1.3 Noncovalent HA Nanoparticles

In biomedical applications, supramolecular vesicles/particles within a nanoscale size have been developed for intracellular drug delivery. Different from covalent nanoparticles, supramolecular amphiphiles could act as the driving force for the vesicles/nanoparticles formation, which was fabricated by functions of the host-guest inclusion during the vesicles/nanoparticles formation process [23]. For the convenience of introduction of HA as targeting and biocompatible units into series of nanoplatforms without tedious synthesis work, β-CD-modified HA (HACD) and adamantane-modified HA (HA-ADA) with different HA chains were developed as building blocks. The synthetic routes are available and mature, and host-guest supramolecular interactions are employed for implant of HA into well-designed systems in a facile way.

In 2013, Yu Liu's group firstly synthesized HACD for targeting drug delivery [24]. β-CD was grafted onto HA backbone in aqueous solution to obtain HACD by a simple one step amide condensation reaction. Then, in aqueous solution, prepared adamantane-modified cisplatin (adamplatin) prodrug was included into cavity of β-CD to obtain HACD/adamplatin complex. The amphiphilic supramolecular complex finally self-assembled to form HAP nanoparticles, which had

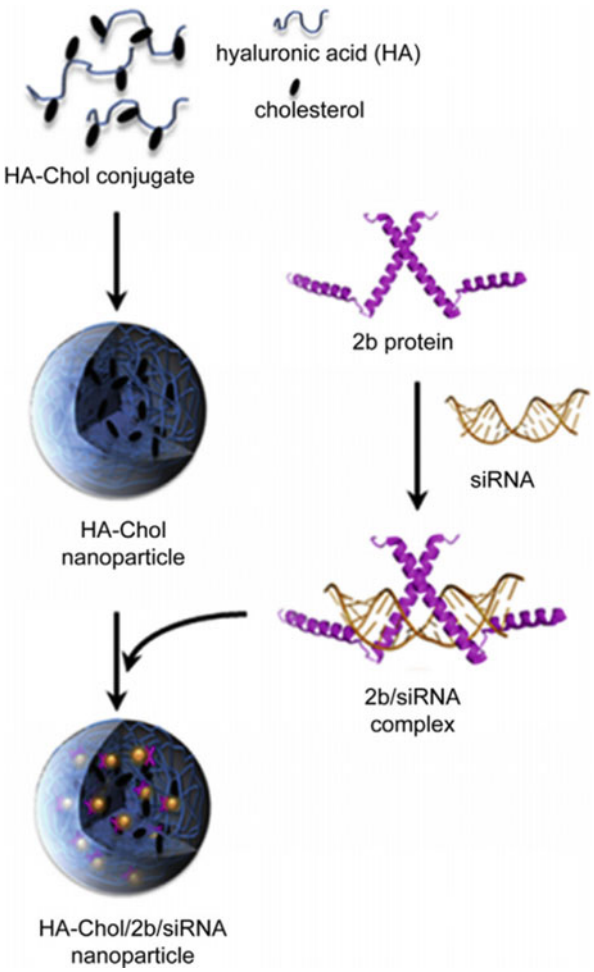

Fig. 15 The construction illustration of HA-Chol/2b/siRNA nanoparticle. (Copyright 2014, Elsevier)

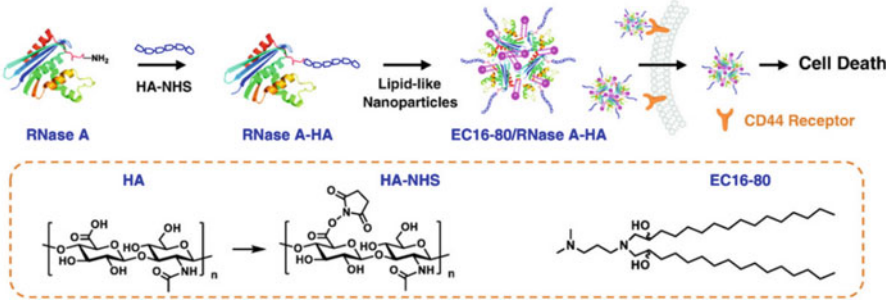

Fig. 16 Schematic illustration of the lipid-like nanoparticles EC16-80/RNase A-HA. (Copyright 2017, Elsevier)

hydrophobic anticancer drug core and hydrophilic HA shell. The HA shell of HAP could recognize overexpressed CD44 receptor on cancer cell surface, and adamplatin prodrug could be released in cancer cells and tissues in vitro and in vivo (Fig. 17). Therefore, similar strategy was also performed to fabricate HA-based nanoparticles for drug delivery, such as HATXP [25] composed of permethyl-β-cyclodextrin-modified HA (HApCD) and porphyrin-modified paclitaxel prodrug (PorTaxol); HACPTPs [26] composed of β-CD-modified camptothecin (CPT-CD) and adamantane-modified HA (HA-ADA); and PTX@DTCD·HAADA [27] composed of HA-ADA, disulfide-containing bridged bis(β-CD)s (DTCD), and crude paclitaxel. The chemotherapeutic drug paclitaxel and Camptothecin could be internalize into cancer cells owing to targeted delivery of HA supramolecular nanoparticles. The same group [28] constructed supramolecular nanoparticle from tetraphenylethylene-bridged β-CD (TPECD) and adamantyl-grafted HA (HA-AD) using the same supramolecular strategy. The TPECD-HAAD nanoparticle emitted stronger fluorescence due to the aggregation-induced emission (AIE) effect. Moreover, the hydrophobic core of TPECD-HA-AD nanoparticle could also load chemotherapeutic drug doxorubicin for targeted drug delivery into cancer cells.

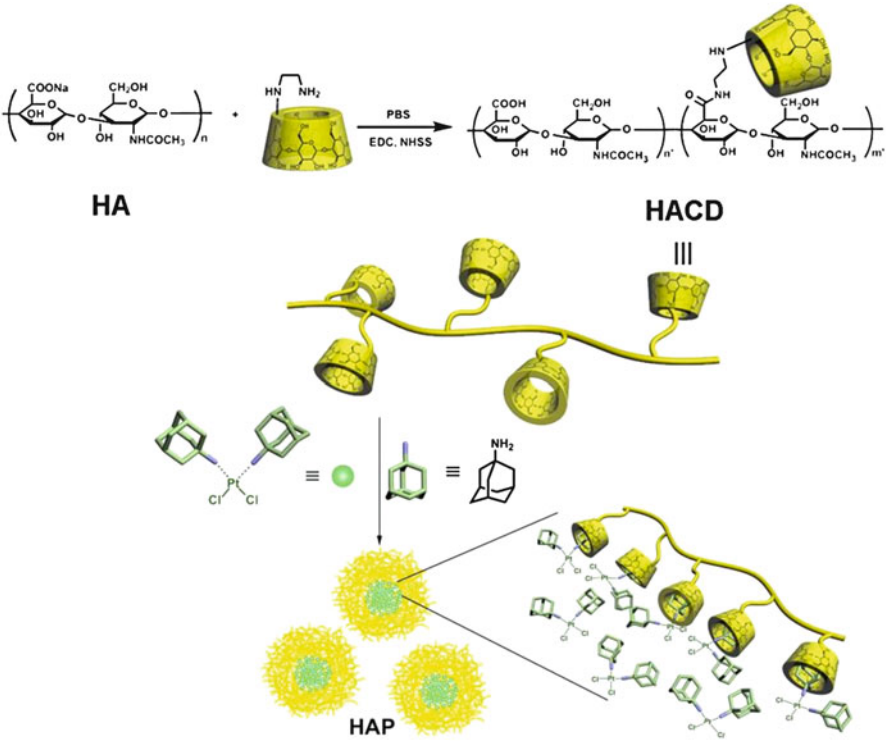

Fig. 17 The construction process of HAP nanoparticles. (Copyright 2013, American Chemical Society)

Similarly, they also reported a water-soluble and biocompatible nanographene/polysaccharide supramolecular assembly (CHBC-2/HA-AD) fabricated through noncovalent interactions between HA-AD and β-CD-modified hexa-cata-hexabenzocoronene (CHBC-2) [29]. Possessing a small size and C3-symmetrical rigid fluorescent nanographene, the CHBC-2 was synthesized from β-CD and hexa-cata-hexabenzocoronene through a click reaction, presenting good luminescence properties and enhanced encapsulation and loading efficiency. Moreover, the CHBC-2/HA-AD supramolecular nanoparticles could noncovalently load anticancer drugs and display not only fluorescence imaging ability toward cancer cells but also higher antitumor activity and lower toxicity than the free DOX, utilizing as a safe and promising targeted drug delivery platform (Fig. 18).

On the other hand, HA supramolecular nanoparticles could be also used for gene delivery. For instance, Yu Liu et al. [30] fabricated ternary polysaccharide nanoparticles composed of HACD, adamantane-bis(diamine) conjugate (ADA), and cucurbit[6]uril (CB[6]) through supramolecular interactions as β-CD/adamantane and positively charged diamine/CB[6] interactions. The positive macrocycle-induced pK_a shift by CB[6] could promote the cation density on bis(diamine) chains, which could facilitate the subsequent siRNA binding. The obtained ternary nanoparticles binding with siRNA acted as supramolecular non-viral vector to targetedly

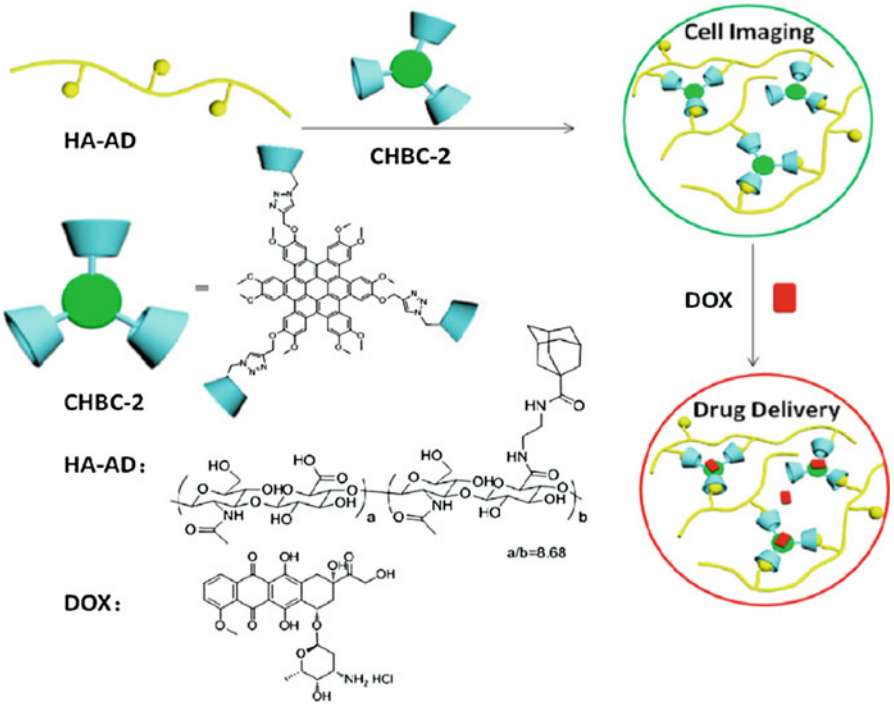

Fig. 18 Construction of DOX@CHBC-2/HA-AD supramolecular assembly. (Copyright 2016, American Chemical Society)

deliver the siRNA into PC-3 cancer cells to silence the exogenous N1-EGFP-pDNA. On the other hand, the biocompatible shell of HA and isolation of positive charged bis(diamine) by CB[6] could greatly decrease the cytotoxicity of the nanoparticle, which might be considered as attractive candidate for capture and release of pharmaceutical nucleic acids in high efficient and safe way (Fig. 19).

Moreover, HACD and doubly positively charged quaternary ammonium group-modified adamantane (ADA2+) were mixed together to generate ADA2+@HACD nanoparticles, which had negatively charged HA shell and positively charged quaternary ammonium chain core to combine plasmid DNA (pDNA). When the neutral ester group on ADA2+ was hydrolyzed to negatively charged carboxyl group, the "zwitterionic" structure with a positive charge and a negative charge on one chain was obtained, and then the condensed pDNA could be released (Fig. 20).

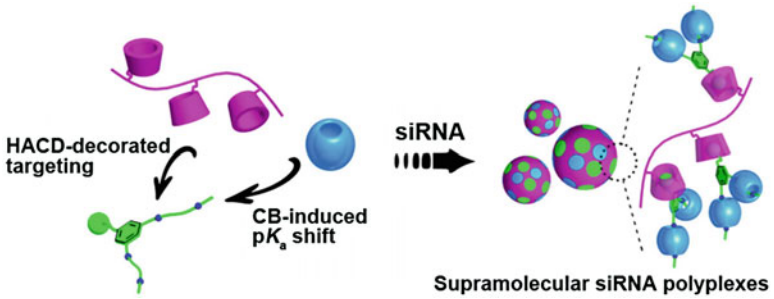

Fig. 19 The construction of ternary supramolecular nanoparticle composed of HACD, ADA, and CB[6]. (Copyright 2016, Nature Publishing Group)

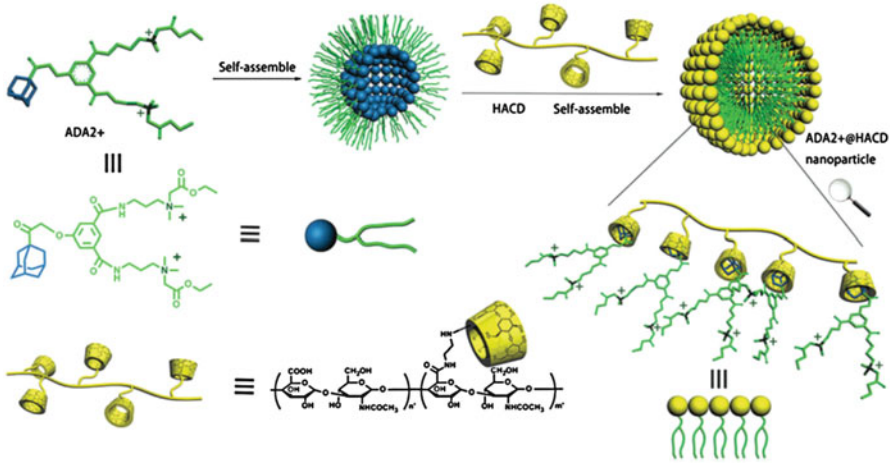

Fig. 20 The preparation process of ADA2+@HACD nanoparticles. (Copyright 2018, The Royal Society of Chemistry)

Yanli Zhao et al. [31] also employed HACD as supramolecular building blocks to construct reduction-sensitive fluorescence-enhanced polymeric nanoparticles for photothermal therapy and chemotherapy. Firstly, chemotherapeutic camptothecin and fluorescent naphthalimide were co-linked onto adamantane to obtain Nap-CPT-Ad in a covalent way. Then the supramolecular interactions and supramolecular amphiphilic interactions would induce HACD/Nap-CPT-Ad complex to form polymeric nanoparticles, which had hydrophilic HA shell and hydrophobic Nap-CPT core. The hydrophobic core of nanoparticles could load photosensitizer IR825 for photothermal therapy under near-infrared (NIR) laser irradiation, and Camptothecin and naphthalimide could be released through disulfide bond cleavage by glutathione (GSH). Then the enhanced fluorescence and photothermal/chemotherapeutic effects could be observed in cancer cells in a targeted way (Fig. 21).

Xiaopeng Han et al. [32] developed a new double-hydrophilic copolymer HA-HPCD by conjugating HP-β-CD (HPCD) with HA, which was further PEGylated

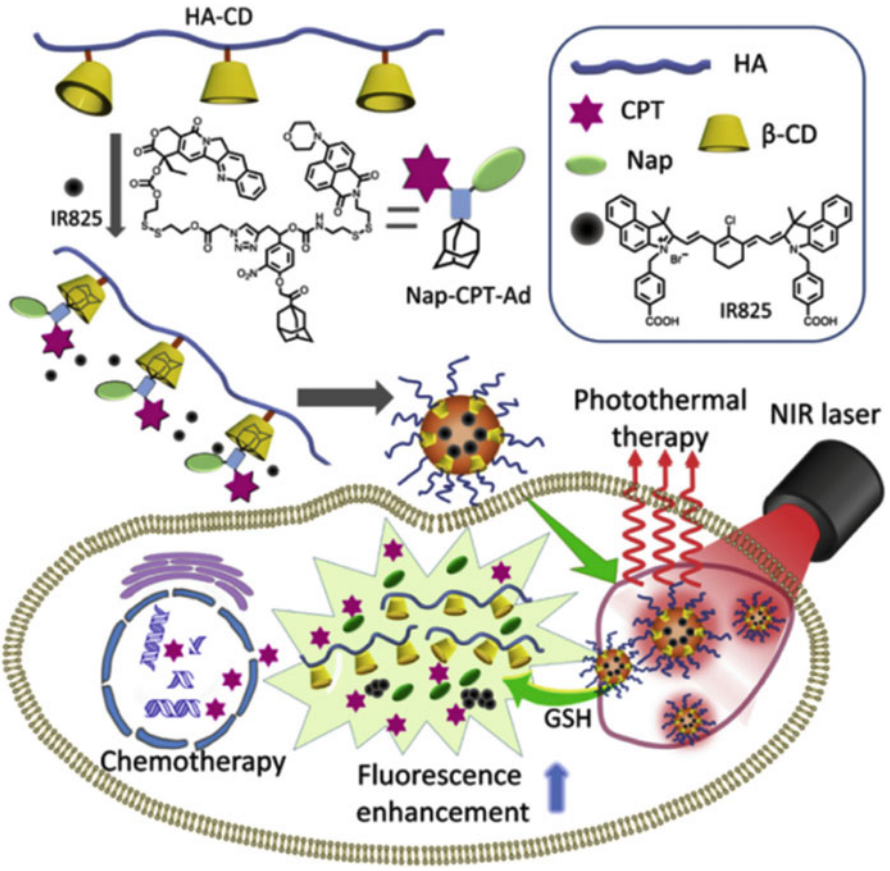

Fig. 21 Schematic illustration of reduction-sensitive fluorescence enhanced polymeric nanoparticles for combinational photothermal-chemotherapy of cancer cells. (Copyright 2018, Elsevier)

with adamantyl-PEG (ADA-PEG) to form inclusion complex HA-HPCD/ADA-PEG, termed as HCPs. Then the PEGylated supramolecular nanoassemblies HA-NPs were fabricated by host-guest and polar interactions between HCPs and DOX, with vitamin E succinate (VES) as a nanobridge. Despite the active recognition between HA and CD44 receptor, the cellular uptake and targeting efficiency of HA-NPs decreased with the increasing PEG density, demonstrating that HA was partly buried by high-density PEG coating. However, the high density of PEG coating was beneficial to long circulation time, tumor biodistribution, and anticancer activity in vivo. Therefore, the well-balanced HA-NPs with 5% PEG coating had the optimal cellular targeting efficiency in vitro and anticancer effects in vivo, revealing that balancing long circulation property and cellular uptake is important to achieve the optimal antitumor efficacy (Fig. 22).

For another, HA could be adhered onto nanoparticles' surface to improve the biocompatibility and targeting effects. Yu Liu's group [33] planted adamantane group onto gold nanoparticles' (AuNPs) surface through Au-S bond. After adding HACD, supramolecular interaction between β-CD and adamantane facilitates the formation of nanocluster HACD-AuNPs, which could load and release series of anticancer drugs, such as doxorubicin, paclitaxel, camptothecin, irinotecan, and topotecan. Next, HACD was employed to modify quantum dots (QDs) [34]. When HACD and CdSe/ZnS QDs interacted in aqueous solution, the remaining carboxyl groups on the HA backbone could be utilized in the ligand-exchange reaction to solubilize and stabilize CdSe/ZnS QDs in water. After further encapsulating

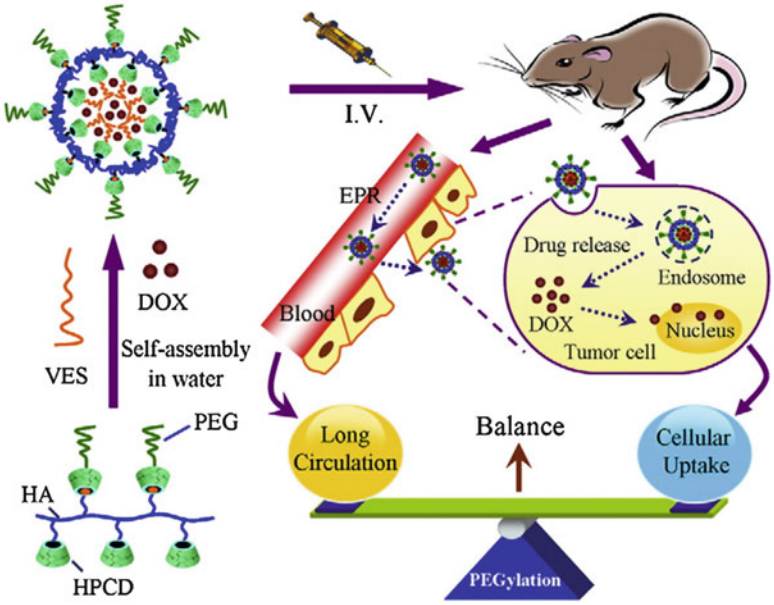

Fig. 22 Schematic diagram of self-assembly of HA-NPs and biodistribution in vivo. (Copyright 2015, Elsevier)

adamantane-modified anthracene (ADA-AN), the generated QDs-HACD/ADA-AN supramolecular nanoparticles possessed low cellular cytotoxicity and showed controlled DNA condensation and targeted cellular imaging abilities toward cancer cells (Fig. 23).

Then, the same group [35] reported a facile method to stabilize fullerene in aqueous solution by constructing water-soluble polysaccharide-porphyrin-fullerene supramolecular conjugates through supramolecular and π-π stacking interactions of triphenyl Zn-porphyrin-modified β-CD, adamantyl-modified HA and C_{60}. Significantly, these supramolecular conjugates which existed as cross-linked or discrete nanoparticles could completely cleave the closed supercoiled DNA to the nicked DNA under the light irradiation and give high DNA cleavage capability. This approach provides a new access of modifying polysaccharide with functional groups and extends the possible applications in many fields of pharmaceutical chemistry and biological technology. In 2018, Yu Liu's group further constructed supramolecular nanofibers based on HACD and host-guest interactions [36]. As shown in Fig. 24, after covalent connection of mitochondrion-targeting peptide (MitP) onto magnetic Fe_3O_4 nanoparticles (MNP), the obtained MitP-MNP could be cross-linked by

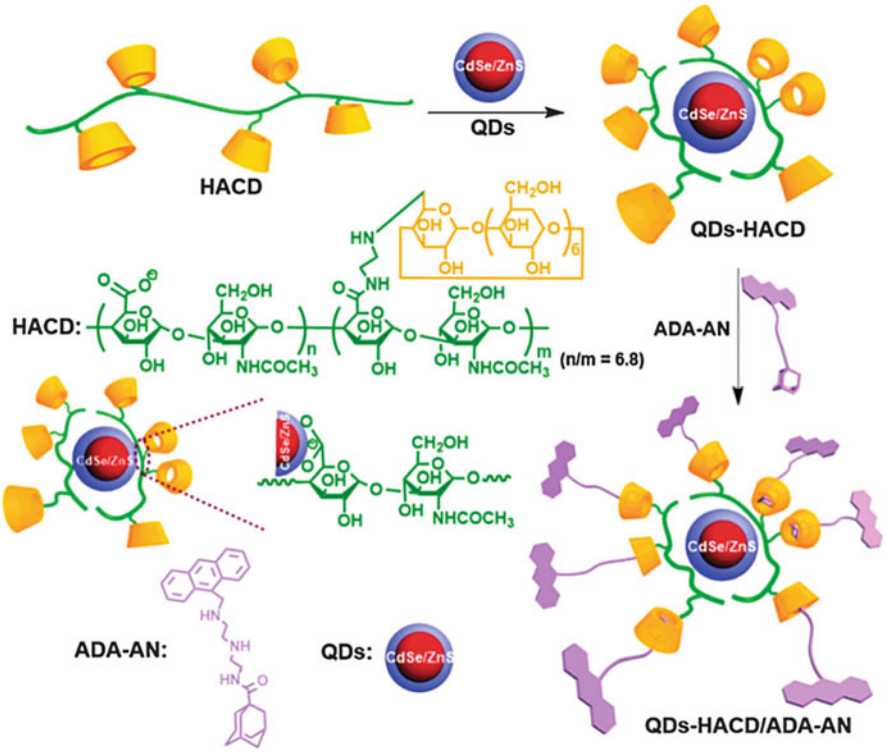

Fig. 23 Construction of QDs-HACD/ADA-AN supramolecular nanoparticle. (Copyright 2016, The Royal Society of Chemistry)

HACD to form MitP-MNP ⊂ HACD nanofiber network through supramolecular inclusion of cyclohexyl group of MitP into β-CD cavity. The prepared MitP-MNP ⊂ HACD nanofiber exhibited photo-triggered and magnetic field-controlled association/directional aggregation properties, which could remarkably suppress invasion and metastasis of cancer cells in vitro and in vivo. Therefore, these geomagnetism- and photo-controlled nanofibers might facilitate the development of intelligently designed biomaterials for cancer therapy.

Xian-Zheng Zhang et al. [37] reported a theranostic nanoplatform using layer-by-layer supramolecular assembly strategy. Firstly, bioreductive prodrug tirapazamine (TPZ) was loaded into aminated mesoporous silica nanoparticles (MSNs), and then per-*O*-methyl-β-cyclodextrin-grafted hyaluronic acid (HA-pmCD) and Gd^{3+}-coordinated 5,10,15,20-tetrakis(4-sulfonatophenyl)-porphyrin ($TPPS_4$) were alternately deposited onto surface of TPZ@MSN through electrostatic interaction and supramolecular interaction. The obtained biocompatible TPZ@MCMS nanoparticle could be specifically internalized by CD44 receptor-positive SCC-7 and MCF-7 cancer cells and release TPZ and $TPPS_4$ by upregulated hyaluronidase trigger effect. Therefore, TPZ@MCMS nanoparticle could not only act as NIR fluorescence and MR imaging system but also synergistically kill cancer cells using generated toxic $^1O_2$ of PDT and activated TPZ radicals under laser irradiation in vitro and in vivo (Fig. 25).

Finally, HA could be utilized for stability and solubility improvement of graphene oxide (GO) nanosheets [38]. In a typical process, β-CD was covalently connected

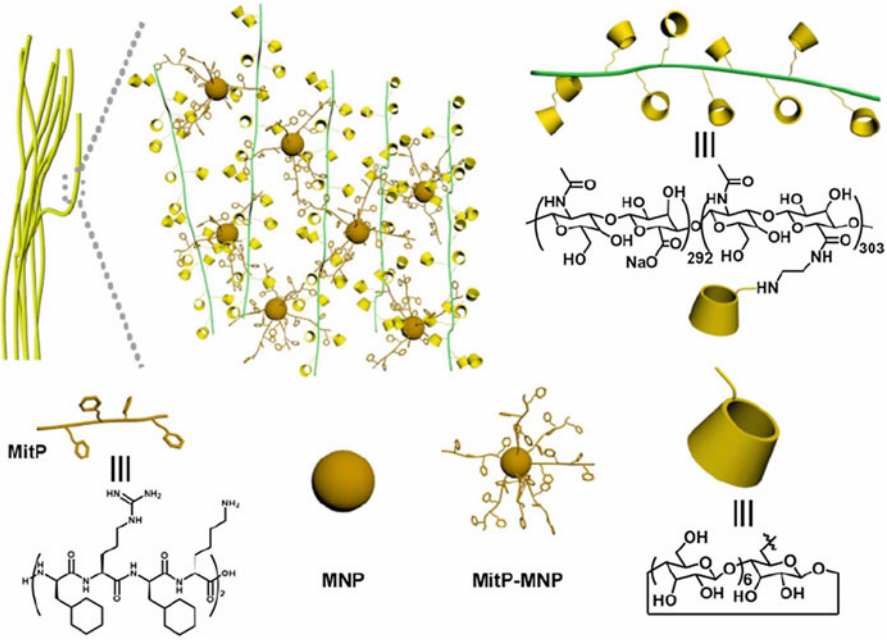

Fig. 24 Schematic illustration of the formation of MitP-MNP ⊂ HACD nanofiber. (Copyright 2018, American Association for the Advancement of Science)

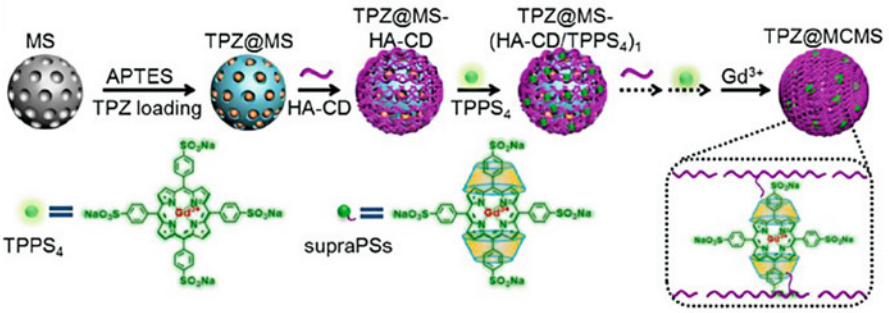

Fig. 25 Layer-by-layer assembly process of TPZ@MCMS nanoparticle. (Copyright 2017, Elsevier)

onto the surface of GO, which could bind camptothecin through π-π stacking interactions. Then HA-ADA was added to cover the surface of GO to enhance targeting capability and assembly stability in the serum environment. Cellular experiments revealed that the prepared CPT@GO-CD-HA-ADA assembly showed higher inhibition effect toward malignant cells than free drug without causing serious side effects (Fig. 26).

52.3.2 HA-Based Supramolecular Hydrogels

Hydrogels are three-dimensional cross-linked networks of hydrophilic polymers, which can hold a large amount of water via surface tension or capillary effect to maintain their structural integrity [39, 40]. In recent research, HA could be widely used in hydrogel construction due to the biocompatibility, biodegradability, mechanical stability, deformability, transparent property, and hydrogen bond nature [41, 42]. Therefore, HA hydrogels with mechanical property similar to human tissues have exhibited great potentials for various biomedical applications including tissue regeneration, drug delivery devices, and wound dressing [43–46]. Two kinds of molecular cross-linking strategy were commonly used in hydrogel preparation: covalent and noncovalent way. Covalent connections by chemical bond usually result in relatively fragile hydrogels without good transparency. Such kind of gels cannot be recovered once the cross-linking connection is broken [47]. In contrast, noncovalent cross-linking, for instance, electrostatic interaction, metal-ligand complexation, hydrogen-bonding interaction, and especially host-guest interaction, could generate reversible and injectable hydrogels with stimuli-responsive and self-healing properties [48].

By digging the biological application of HA hydrogel, Mikyung Shin and Haeshin Lee [49] reported an injectable HA hydrogel through hydrogen bond interactions for loading of protein. Gallol was firstly grafted onto HA backbone (HA-Ga), and then cross-linking occurred as oligo-epigallocatechin gallate (OEGCG) was added to interact with HA-Ga through hydrogen bond from both gallol-to-gallol and gallol-to-HA interactions. This gallol-involved cross-linking is

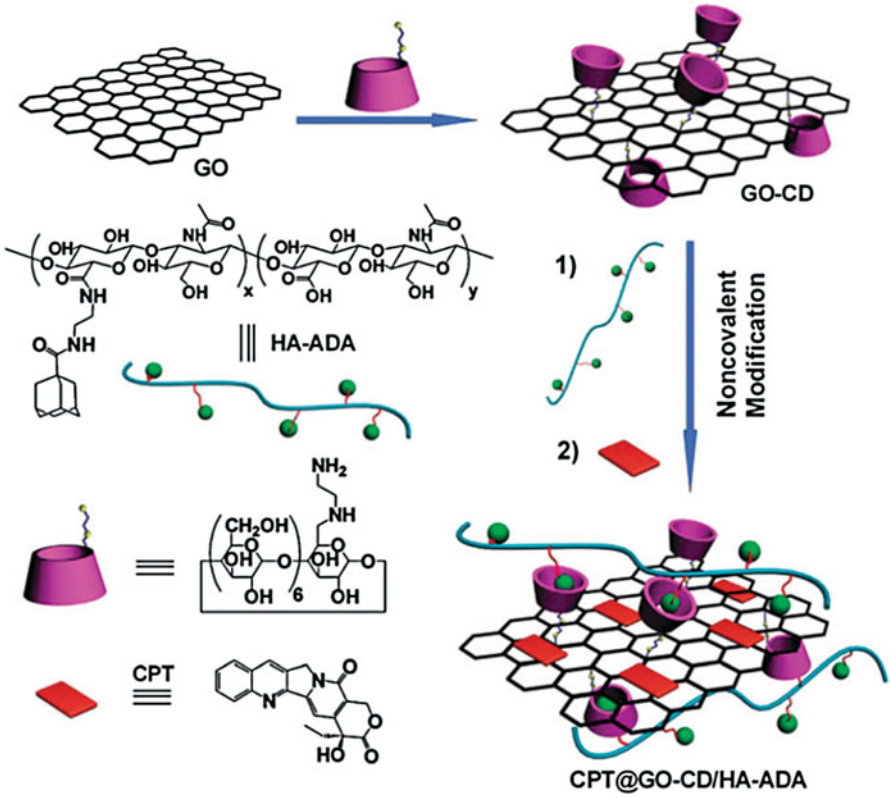

Fig. 26 Construction of CPT@GO-CD-HA-ADA supramolecular assembly. (Copyright 2014, The Royal Society of Chemistry)

reversible and shear-thinning, which made the hydrogel injectable. The gallol portion in hydrogel possessed superior capability on binding proteins via non-covalent interactions. Therefore, the prepared gallol-rich hydrogel exhibited spontaneous enrichment of proteins from aqueous solution and enzymatic degradation resistance capability (Fig. 27).

Besides, Oren A. Scherman et al. [50] reported another facile strategy to construct HA hydrogel. Phenylalanine functionalized HA (Phe-HA) was cross-linked by cucurbit[8]uril (CB[8]) through strong 1:2 "homoternary" complexes with the pendant Phe residues. This methodology was reproducible and translatable to a variety of polysaccharides, and supramolecular hydrogel based on phenylalanine modified carboxymethyl cellulose (Phe-CMC) and CB[8] were also investigated (Fig. 28).

The employment of cucurbituril-based supramolecular interaction for hydrogelation was also reported by Kimoon Kim et al. [51, 52]. Cucurbit[6]uril (CB[6]) and diaminohexane (DAH) were, respectively, grafted onto HA to form CB [6]-HA and DAH-HA. Besides, the author also synthesized dexamethasone modified CB[6] (Dexa-CB[6]) to load drug into hydrogel matrix. Then the hydrogel was

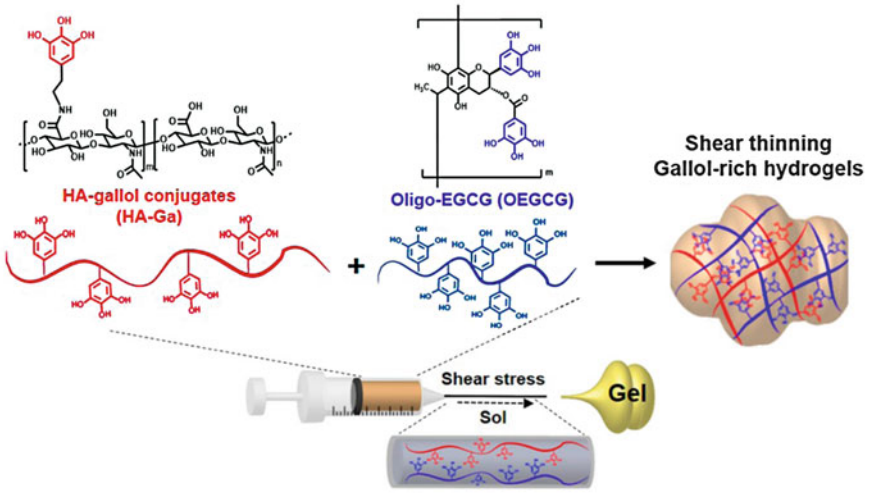

Fig. 27 Construction process of gallol-rich hydrogels. (Copyright 2017, American Chemical Society)

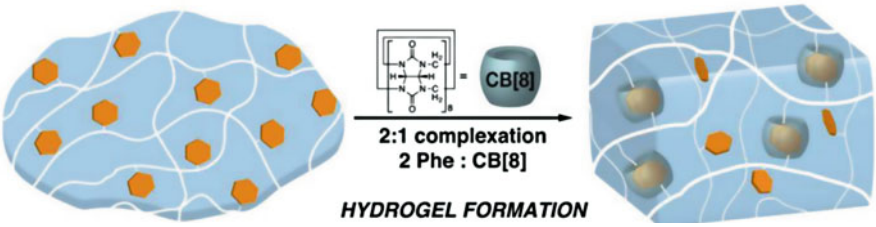

Fig. 28 Supramolecular 1:2 "homoternary" complex-induced gelation process. (Copyright 2015, American Chemical Society)

formed through cross-linking by CB[6] and DAH supramolecular interaction. The obtained hydrogel with loaded dexamethasone and transforming growth factor-β3 (TGF-β3) could package human mesenchymal stem cells (hMSCs) for the formation of neocartilage in vivo (Fig. 29).

Adrianne M. Rosales et al. [53] reported a biomimetic hydrogel with reversible modulation property based on HA and supramolecular interactions. When the synthetic *trans*-azobenzene modified HA and β-CD-HA were mixed together, supramolecular interaction induced the inclusion of *trans*-azobenzene into β-CD cavity, and the cross-linked stiff hydrogel was obtained. After irradiation with 365 nm UV light, the *trans*-form of azobenzene was isomerized to *cis*-form, which would slip out of β-CD cavity, and the cross-link density of the gel decreased to form soft hydrogel. Therefore, this supramolecular hydrogel was light modulated and made reversible changes in cross-link density for release of encapsulated proteins. This work illustrated that HA hydrogel would have great potential in drug delivery,

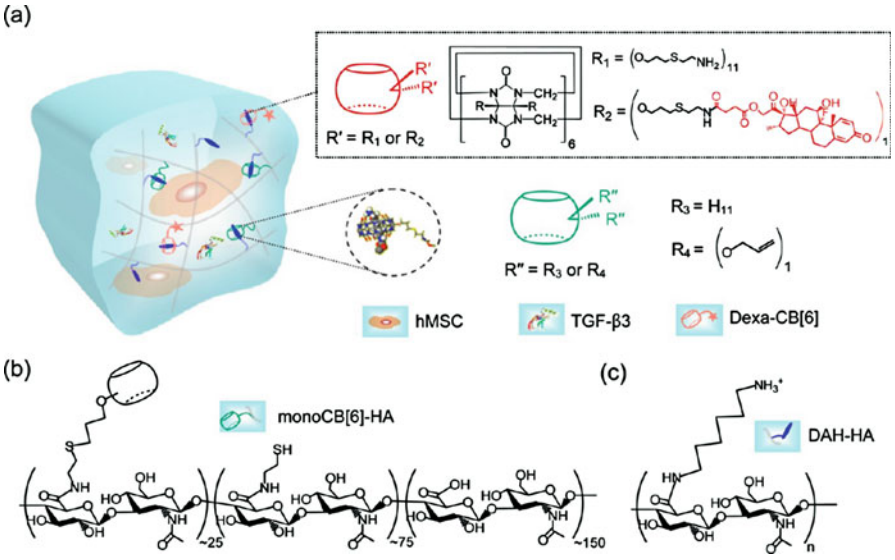

Fig. 29 Supramolecular CB[6]/DAH-HA hydrogels encapsulating hMSCs and TGF-β3 with modularly modified Dexa-CB[6] by the strong supramolecular interaction between CB[6] and DAH. (Copyright 2014, American Chemical Society)

mechanobiology studies, cellular mechanosensing, and tissue engineering fields (Fig. 30).

However, in the opinion of Prof. Liming Bian, the traditionally prepared biopolymer-based supramolecular hydrogels cross-linked by host-guest interactions are mechanically weak and can't be maintained as "freestanding 3D constructs." Thus, he and his co-workers [54] described a novel host-guest macromer (HGM) approach for freestanding supramolecular hydrogels. HGM was firstly formed through supramolecular interaction between adamantane-functionalized HA (AD_xHA) and monoacrylated β-CD (mono-Ac-βCD). Then under irradiation of UV light, polymerization of monoacrylated group in HGM caused cross-linking of hydrogel in multivalent way. The obtained supramolecular hydrogels exhibited significantly reinforced mechanical and self-healing properties. Additionally, the hydrogel's freestanding 3D construction would make it as promising carrier of human mesenchymal stem cells (hMSCs) and proteinaceous growth factors (TGF-β1) for promoting cartilage regeneration in a rat model (Fig. 31).

The similar strategy was also reported early by Jason A. Burdick et al. [55, 56], who synthesized adamantane-modified HA (Ad-HA) and β-CD-modified HA (CD-HA) as building blocks, and host-guest interactions of β-CD with adamantane were employed as the binding force of the hydrogel cross-linking [57]. The obtained HA hydrogel was of shear-thinning property and could near-instantaneously reassemble for material retention at the target site without erosion. Moreover, besides supramolecular interaction, the authors also introduce secondary covalent cross-linking among the polysaccharide chains to increase the hydrogel's moduli and stability,

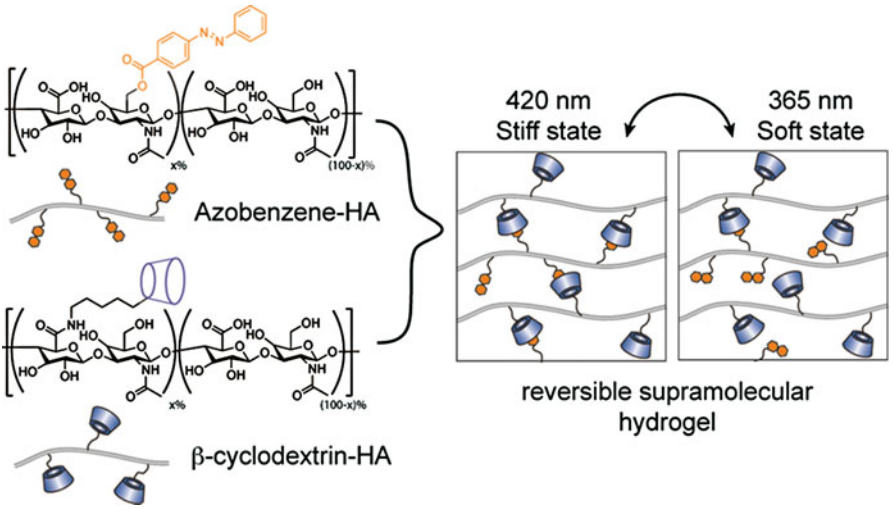

Fig. 30 The modulation process of reversible supramolecular hydrogel controlled by 365 and 420 nm light. (Copyright 2018, American Chemical Society)

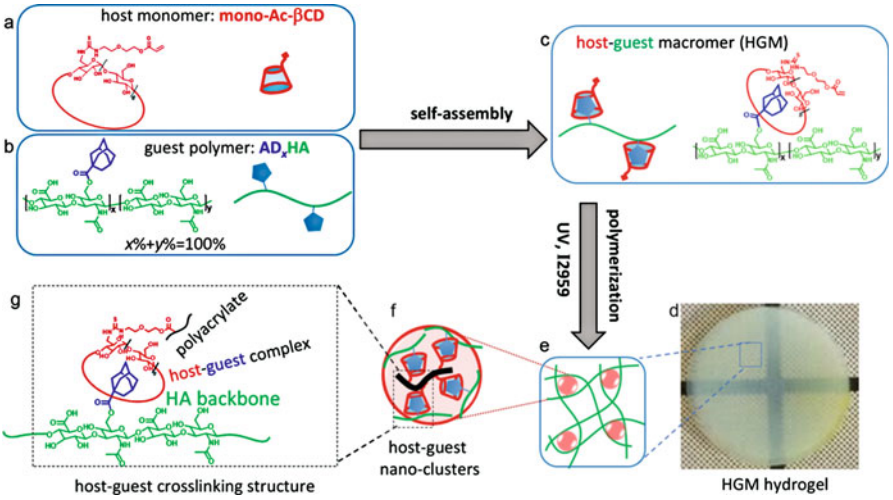

Fig. 31 The synthetic routes of HGM hydrogels. (Copyright 2016, American Chemical Society)

such as methacrylates and thiols/dithiothreitol with Michael acceptors [58–60]. Using similar strategy, the same group [61] also synthesized β-CD and methacrylate-modified HA (CD-MeHA) and Ad-HA. The cross-linking of CD-MeHA fibers via radical polymerization of methacrylates would result in the formation of CD-MeHA hydrogels. Next, the two CD-MeHA nanofibers were adhered to each other by adding Ad-HA aqueous solution, and macroscopic assembly induced by

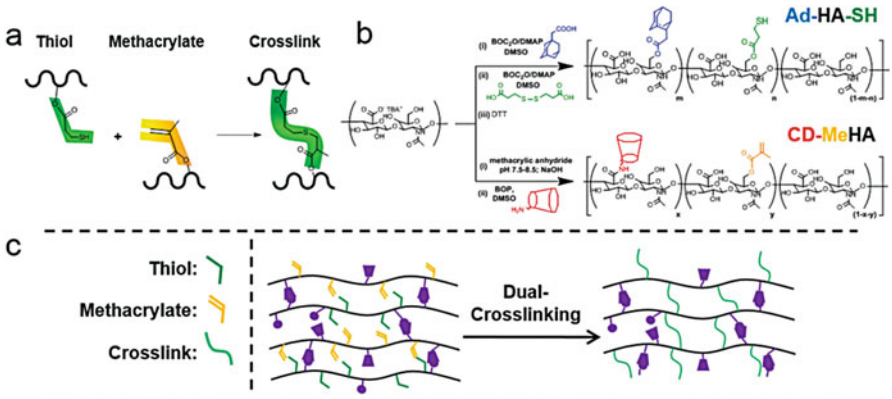

Fig. 32 The formation of HA hydrogel cross-linked by Ad-HA-SH and CD-MeHA. (Copyright 2014, The Royal Society of Chemistry)

supramolecular interactions was realized and could be observed by naked eyes. The obtained multilayered scaffolds were applied for cell culture or tissue engineering (Fig. 32).

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