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Recent Advances in Self-assembled Nano-therapeutics

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Abstract The applications of nanotechnology in biomedicine have gained considerable attentions in recent years owing to the great enhancement of therapeutic efficiency. Integration of self-assembly into nanotechnology has brought tremendous convenience during the formation of nano-carriers. Based on distinctive methods of self-assembly, nano-therapeutics have been developed to an impressive stage with the ability to perform site-specific delivery with temporal and spatial control. This review focuses on the recent advances in the preparing methods for nano-therapeutics, and their applications in the treatments of diseases.

Keywords Self-assembly; Nano-therapeutics; Hydrophobic effect; Electrostatic interaction; Supramolecular host-guest interaction

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INTRODUCTION

Human health is threatened by multifarious diseases attributed to autologous stressed cells or exogenous infection[1]. A mass of medicines were put in use to directly kill these abnormal cells and infections, as well as regulate the disordered metabolism to help body to return to normal[2, 3]. However, the traditional pharmaceutical therapies always suffer from a low therapeutic efficiency and high tissue toxicity *in vivo*[4]. It is essential to develop a promising method to assist therapeutic agents to play a more efficient and safe role in disease treatment.

Nanotechnology has been demonstrated to be a promising drug-transporting manner since the first lipid drug delivery nano-system was described in 1960s[5]. Taking advantages of nanotechnology, the nanoscale medicines can achieve[6] (1) improved solubility of poorly water-soluble drugs; (2) prolonged half-life of drugs by reducing immunogenicity; (3) transcytosis across tight epithelial and endothelial barriers; (4) intracellular delivery of large macromolecule drugs; (5) controllable release of drugs at a sustained rate or in an environmentally responsive manner; (6) co-delivery of two or more drugs or therapeutic modalities for combination therapy; (7) visualization with imaging modalities. As a result, a bulk of nanoscale pharmaceuticals have been exploited and burst into the explosive growth and revolution in following years[7–10].

Generally, a stable medicine-containing nanoscale structure can be fabricated by (1) conjugation or absorption on a nanoparticle; (2) permeation into a porous material or a three-dimensional network like hydrogel; (3) encapsulation into nano-devices by self-assembly. Compared to the first two methods, the self-assembled nano-devices for therapeutic drug delivery have received more widely attentions because diverse unprecedented structures and patterns can be easily formed by self-assembly with extreme efficiency and precision[11]. Self-assembly refers to the process that a host of initially disordered components spontaneously organize to a more ordered one without intervention by external influence, which can occur at all length scales from millimeter to nanometer scales[12]. The forces driving the assembly of molecules, polymers and colloids into an organized system can be expanded beyond the conventional ionic, covalent, metallic, hydrogen and coordination bonds, to include weaker interactions like van der Waals force, electrostatic and hydrophobic interaction, magnetic, π-π and optical forces, *etc*[13]. The innovations of integrating self-assembly with therapeutic drug-loaded nano-devices can (1) make the formation process more convenient; (2) precisely administrate the sizes, shapes or surface properties; (3) endow them with a good stability and multifunction for future use[9]. To date, various self-assembled nano-systems have been explored for therapeutic purpose to carry the drugs into body in controlled manners from the sites of administration to the therapeutic target, to improve therapeutic efficiency maximally[14]. This review concentrates on the recent advances in the self-assembled nano-systems for human disease treatments. A set of self-assembled methods during the fabrication progress will be discussed in the second part, and numerous fascinating researches related to the achievements of nano-system to therapy in cancers, metabolic and infectious diseases will be reviewed in the third part to highlight the applications of self-assembled systems in biomedicine.

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METHODS OF SELF-ASSEMBLY IN NANO-SYSTEM

Over the past decades, self-assembly has been widely utilized to fabricate drug-delivering carriers and biomedical devices (Table 1). To meet the requirements of clinical settings, it is essential to employ appropriate self-assembly strategies to achieve desired features such as sufficient drug-loading, responsive drug release, targeting capability, *etc*. To date, various types of self-assembly strategies have been developed to achieve the construction of functional nanostructures driven by various intermolecular forces including hydrophobic

Table 1 Recent advances in self-assembled nano-therapeutics

Drug	Material	Implementation type	Application	Development status	Ref.
Doxorubicin	PAE-*b*-PCL	Hydrophobic interaction	Liver cancer	Preclinical study	[132]
Doxorubicin	PEG-PLys/PBA	Hydrophobic interaction	Liver cancer	Preclinical study	[38]
Doxorubicin	PAE-*b*-P(Lys)	Hydrophobic interaction and hydrogen-bond interaction	Liver cancer	Preclinical study	[134]
Doxorubicin	PEG-*b*-PPC	Hydrophobic interaction and chemical covalent bond	Cancer stem cells and mammary cancer	Preclinical study	[35]
Irinotecan and Chlorambucil	Amphiphilic drug-drug conjugate	Hydrophobic interaction	Mammary cancer	Preclinical study	[56–58]
CDK4 mRNA	PEG-D_m-PCL	Hydrophobic interaction and electrostatic interaction	Non-small cell lung cancer	Preclinical study	[138]
Plasmid DNA	PEI	Electrostatic interaction and chemical covalent bond	Colon cancer	Preclinical study	[139]
GAL4-VP16 transcription factor	CD-PEI and Ad-PEG	Host-guest interaction and electrostatic interaction	Cancer	Preclinical study	[144]
Doxorubicin	PAA-CD and Ad-PEG	Host-guest interaction	Ovarian and mammary cancer	Preclinical study	[104]
Caspase-3	AAm and APm (nanogel)	Electrostatic interaction and hydrogen-bond interaction	Mammary cancer and melanoma	Preclinical study	[117]
Recombinant maltose-binding protein fused apoptin	AAm and APm (nanogel)	Electrostatic interaction and hydrogen-bond interaction	Mammary cancer	Preclinical study	[120]
AS-miR-21	AAm and APm (nanogel)	Electrostatic interaction	Mammary cancer	Preclinical study	[122]
Doxorubicin	Liposome	Hydrophobic interaction	Metastatic breast cancer, ovarian cancer, non-small cell lung carcinoma, melanoma, and Kaposi's sarcoma	FDA approved (Doxil®)	[146–150]
Paclitaxel	Liposome	Hydrophobic interaction		FDA approved (LEP-ETU, EndoTAG®-1, Lipusu®)	
L-asparaginase	PEG-liposome	Hydrophobic interaction	Acute lymphoblastic leukemia	FDA approved (Oncaspar®)	[151]
Doxorubicin	Fusogenic liposome	Hydrophobic interaction and hydrogen-bond interaction	Mammary cancer	Preclinical study	[156]
Insulin	PEG-*b*-P(AA-*co*-AAPBA)	Hydrogen-bond interaction and chemical covalent bond	Diabetes mellitus	Preclinical study	[164]
Insulin	PNIPAM-*b*-P(Asp-*co*-AspPBA)	Hydrophobic interaction and chemical covalent bond	Diabetes mellitus	Preclinical study	[166]
None	PEG-*b*-PCL and PEG-*b*-PNIPAM	Hydrophobic interaction	Alzheimer’s disease	Preclinical study	[178]
None	PEG-*b*-PCL and PEG-*b*-PAE	Hydrophobic interaction	Alzheimer’s disease	Preclinical study	[185]
Amphotericin B	Liposome	Hydrophobic interaction	Fungi infections	FDA approved (AmBisome®)	[203, 204]
Benzyl penicillin	Liposome	Hydrophobic interaction	*Staphylococcus aureus*	Preclinical study	[205]
Saquinavir	PEG-*b*-PCL	Hydrophobic interaction	HIV-1/AIDS	Preclinical study	[211]
Halofantrine	PEG-*b*-PLA	Hydrophobic interaction	Malaria	Preclinical study	[212]
Triclosan	PEG-*b*-PAE	Hydrophobic interaction and electrostatic interaction	Biofilm recalcitrance	Preclinical study	[213]
Vancomycin, gentamicin or quinupristin	PEG-*b*-PP and PEG-*b*-PC	Hydrophobic interaction	Penicillin G-resistant bacterial strains	Preclinical study	[214]
Antimicrobial peptides	PEI	Electrostatic interaction and chemical covalent bond	*P. aeruginosa*	Preclinical study	[215]

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interaction, electrostatic interaction, host-guest interaction, and other non-covalent interactions.

Hydrophobic Effect

Hydrophobic effect is an interaction mediated by water to cause clustering of hydrophobic units, leading to the tendency for oil and water to segregate[15]. This effect is essential for the assembly of amphiphilic molecules in water, which contains hydrophobic as well as hydrophilic components[16]. When amphiphiles are dispersed in water, the hydrophilic segment of amphiphiles preferentially interacts with the aqueous phase while the hydrophobic portion tends to reside in the air or in the nonpolar solvent[16]. Driven by this repulsive force, amphiphiles are able to self-assemble in water to form various well-defined molecular assemblies, such as micelles and vesicles[17]. Remarkably, the structure and size of the assemblies are closely connected to the architecture of the amphiphiles. Owing to the unique property of hydrophobic effect, these amphiphilic assemblies have been in use as drug carriers to stabilize the agents, especially water-insoluble drugs, in aqueous in different forms including polymer micelles, liposomes, and others[17, 18].

Polymeric micelles

This self-assembly of amphiphilic block copolymer to form polymer micelles, driven by repulsion effect of hydrophobic block in the solvent to fold as a core, has immensely attracted attention to be used as a drug delivery system to maximize therapeutic efficiency and minimize the side effects[19–21]. Entrapment of hydrophobic drugs within the micelles stabilizes the drug in aqueous solution, and shields the recognition of mononuclear phagocyte system (MPS) by hydrophilic blocks such as poly(ethylene glycol) (PEG), extending around the hydrophobic core. As a promising replacement of traditional pharmaceutical excipients, the self-assembled amphiphilic block copolymers exhibit many flexible and elaborate properties to bring much convenience to design for various drug therapeutics and intricate delivery environment[22, 23]. For instance, the size of block copolymer micelles can be tuned to a nanometer scale (50–200 nm) *via* controlling the molecular weight of polymer blocks to escape the elimination of liver and kidney[24]. The ideal choice of hydrophobic blocks including poly(propylene oxide) (PPO), poly(amino acid)s ((PLAA)s), poly(ester)s, polyamines or poly(amine ester)s depends on the individual molecular structure and property of drugs[22, 23, 25]. Making full use of these superiorities, polymer micelles can introduce several major intrinsic characteristics to incorporated therapeutic agents, *e.g.*, drug aqueous solubility, *in vivo* stability, pharmacokinetics and biodistribution[20, 26, 27].

An obvious problem with conventional polymer micelles is the requirement of different surface properties to cross multiple barriers during delivery process[28, 29]. For example, PEG shells can prolong blood circulation half-time *via* shielding the elimination of MPS, in the meanwhile preventing the drug uptake by tumor cells when delivering drug intravenously[30, 31]. Aiming at handling this contradictory, multifunctional polymer micelles were constructed to adapt varied environment by changing their surface properties, sizes or others under the stimulation of surroundings (*e.g.*, pH, temperature, enzymes, *et al.*)[32–34]. Wang *et al.* utilized the pH responsiveness of 2-propionic-3-methylmaleic anhydride (DMMA) as the bridge to link the hydrophilic (PEG) and hydrophobic segment (PCL)[35]. The PEG shell, which was responsible for adapting to blood circulation, was rapidly dissociated *via* breakage of DMMA in acid tumor environment, realizing the enhanced tumor accumulation as well as the postponed blood circulation half-time synchronously.

To date, the therapeutic efficacy was limited by side effects to healthy tissues and multidrug resistance to the tumor cells. Using the micelle to simultaneously deliver multiple drugs to the same destination has become a promising approach owing to its synergistic effect[36, 37]. In Cheng's work[38], a complex micelle composing of doxorubicin (DOX) and (-)-Epigallocatechin-3-O-gallate (EGCG) was constructed through hydrophobic interaction and phenylboronic acid-catechol interaction between poly(ethylene glycol)-block-poly(lysine-*co*-lysine-phenylboronic acid) (PEG-PLys/PBA) and EGCG. Acid cleavability of phenylboronic acid-catechol interaction in micelle core had significant benefits for delivering EGCG and DOX to the same destination with synergistic effects.

Liposomes

Liposomes are colloidal particles assembled by natural or synthetic phospholipids, which contain charged or hydrophilic domain and two hydrophobic fatty acyl chains (tails). In solution, phospholipids attract with each other and align to form contiguous bilayer sheets to entrap solute with a spherical shape. Similar to a membrane, the hydrophobic tails hide inside and hydrophilic domains expose to the aqueous. Liposomes have been used as pharmaceutical carriers to improve therapies because of their stabilizing therapeutic pharmaceuticals, simplifying site-specific drug delivery to tumor tissues, improving cellular uptake *in vivo*[39–41]. From small-molecule drugs to a variety of macromolecules (*e.g.*, nucleic acids, proteins and imaging agents), liposomes exhibit inclusiveness to various drugs regardless of the hydrophobicity[42]. Liposomes can also offer their superiority of size controllability, hypotoxicity, biocompatibility and biodegradability in pharmacotherapy[43]. Thus, liposomes have been evaluated as one of the most established nano-carriers for disease treatment[44–47].

However, liposome-wrapped medicines encounter multiple defense systems in body including reticuloendothelial system (RES), opsonization, and immunogenicity, aiming at recognition, neutralization and elimination of invading substances[39, 43]. These obstacles must be circumvented for an optimal delivery. Conjugation of PEG polymers to the liposomal membrane is a key strategy to prevent the removal by defense systems for improving circulation time[3, 48, 49]. Attributed to the large hydrodynamic volume of the PEG chains, PEGylation of liposomes inhibits both electrostatic and hydrophobic reactions with plasma proteins and cells to reduce the uptake by defense systems[50].

Nowadays researches on therapeutic liposomes tend to introduce functional groups on the surface of liposomes to solve specific barriers or develop combinational therapies to enhance efficiency[51–54]. For example, aiming at improving

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the delivery efficiency of DNA or siRNA, the liposome was combined with polyethylenimine (PEI) to form liposome-PEI complexes in which liposomes worked as the non-toxic shells and PEI as the delivery reagent of DNA or siRNA[55]. To achieve both drug delivery and photothermal therapy, a lipid gold hybrid material (LiposAu) was formed by coating liposome with gold through 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC)-cholesterol, in which gold segment was responsible for photothermal activity and liposome served as drug nano-carriers. Such biodegradable nanoparticle system held great promise in combinational nano-therapeutics against cancer[56].

Drug-drug conjugate

Until now, the vast majority of drug delivery systems require excipient to assemble to nano-carriers to help improve the therapeutic efficiency of the medicines[57–59]. However, Yan *et al.* firstly proposed a new amphiphilic drug-drug conjugate (ADDC) concept with which anticancer drugs could self-assemble to nano-scale particles driven by hydrophobicity of drug without using any excipient. This new drug delivery system would be more efficient because of the integration of the advantages of free drugs and nanomedicine. In this work[60], a water-soluble anticancer drug irinotecan (Ir) and another water-insoluble anticancer drug chlorambucil (Cb) were conjugated together to self-assemble into nano-scale nanoparticles (88 nm) in water. The particle size was suitable for enhanced permeability and retention (EPR) effect, resulting in a good biodistribution. Once uptake by tumor cells, ADDC would be cleaved to release the free drugs *via* the pH response of the ester bond, exhibiting a great antitumor activity. Inspired by this concept, a series of ADDCs were designed for cancer treatment[61–65]. In spite of the tremendous convenience to construction and significant enhancement of therapeutic efficiency, this self-assembled system was faced with the problems of toxicity to organs and rapid clearance by RES. Unfortunately, articles about dealing with this trouble have not been reported up to now.

Electrostatic Interaction

Electrostatic self-assembly is based on physical adsorption actuated by attraction between the opposite charges. Not only charged macromolecules such as polyelectrolytes and nucleic acids, but also charged interfaces or substrates such as proteins, virus and nanoparticles can carry out this process *via* direct mixing[66–69]. Electrostatic self-assembly is applicable to nano-therapeutic due to its convenience in surface decoration and remarkable nano-scale size controlled by pH, ionic strength or polymer functionality and concentrations[70]. Generally, electrostatic self-assembly exhibits two main manners including electrostatic polymeric complexes and layer-by-layer (LbL)[70].

Electrostatic polymeric complexes

The most common method of electrostatic self-assembly is combining the polyelectrolytes or charged polymers with opposite charged blocks together to form electrostatic polymer complexes[71]. Polyelectrolytes include polycations such as poly(ethyleneimine) (PEI), poly(allylamine hydrochloride) (PAH), and polyanions like poly(acrylic acid) (PAA) and poly(styrene sulfonate) (PSS). Other charged polymers contain some natural polymer like positive chitosan, and negative dextran and hyaluronic acid[69].

As is known to all, gene therapy is an effective method to treat many diseases[72, 73]. However, there are many barriers to gene delivery including cellular barriers (intracellular uptake, endosomal escape, DNA release, and nuclear uptake) and extracellular barriers (avoidance of particle clearance mechanisms, targeting to specific tissues and/or cells of interest, and protection of DNA from degradation)[66]. Since gene is negatively charged, cationic polymers are utilized to complex with them *via* electrostatic interaction to enhance the transfect efficiency, protect gene from degradation and mediate cellular entry. These cationic materials include PEI, polyamidoamine (PAMAM), poly(β-amino ester)s (PAE), (diethylamino)ether (DEAE)-dextran and cationic lipids, *etc*[71]. Such self-assembled gene/polymeric complexes have been proved to a high efficacy *in vitro* through a mechanism of electrostatic associations between the positively charged particles and the negatively charged cell surface.

However, one major challenge is that positive charge promotes electrostatic association with negatively charged serum proteins, along with subsequent opsonization and clearance of assembles when introducing *in vivo*[74, 75]. Neutralizing the charge of the cationic nano-assembles is a potential strategy for improving biodistribution[76]. For example, PEGylation and/or covalent attachment of transferrin ligands to polyethylenimine (PEI) can increase gene expression of PEI/DNA particles in distant tumors[75]. Liposome was also used to encapsulate PEI/DNA complexes to increase biocompatibility[55]. However, these methods also potentially decrease gene delivery efficacy on account of reducing charge.

To date, gene/polymer complexes have been developed to target specific cells *in vivo* by conjugating functional groups[77]. For example, Won *et al.* constructed a fusion-oligopeptide gene complex consisting of an adipocyte-targeting sequence (ATS) and 9-arginine (ATS-9R)[78]. ATS could bind to prohibitin located on the adipocyte surface, responsible for targeting adipocytes. *In vivo* study showed that ATS-9R allowed a successful selective transfect of a short-hairpin RNA (shRNA) for silencing fatty-acid-binding protein 4 (shFABP4) in mature adipocytes.

Layer-by-layer assembly

Conventional electrostatic complexes therapy was limited by uncontrollable release and varisized particle sizes. Instead, new therapies deposit drugs on size-uniform particles using a layer-by-layer approach[79]. In the layer-by-layer method, alternating anionic and cationic layers are laid on a particle *via* electrostatic workforce[80]. Compared with traditional drug nano-devices, the layer-by-layer method exhibits advantages of simplicity and chemical mildness because this process can be achieved just by immersing into a solution containing an oppositely charged substance, without the requirement of special conditions. In addition, this method is widely applicable to a variety of topologies and substrates such as gold, glass, liposome, micelles[81–83]. Thus, the broad freedom in structural design of the layer-by-layer assemblies

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makes it possible to deposit various materials on invisible colloidal cores[84–87].

Converting water insoluble drugs into stable aqueous nanocolloids was the main challenge for layer-by-layer assemblies[79]. Lvov and coworkers treated aqueous suspensions of insoluble drugs with powerful ultrasonication to obtain nano-sized cores[88]. Sequential self-assembly of polycations and polyanions on the particle led to an ultrathin polyelectrolyte shell to stable drugs in aqueous with a diameter of 5–50 nm. Utilizing this method, stable nanocolloids of amoxifen and paclitaxel were successfully prepared with high drug content (up to 90 wt%)[89].

In a recent progress, layer-by-layer assembles have been utilized to targeted and co-delivery therapy against tumor. Hammond's group developed a nanoparticle-based platform which could realize the co-delivery of anti-cancer drugs and siRNA[90]. This platform employed uniformly sized, negatively charged, carboxyl-modified and doxorubicin-loaded phospholipid liposome as a model nanoparticle core, poly-L-arginine (PLA) as positively charged polymer. siRNA and PLA were coated on the surface of nanoparticles layer-by-layer alternatively to enhance the delivery efficiency of both siRNA and doxorubicin. Hammond *et al.* also designed a pH-sheddable layer by layer nanoparticle to target hypoxic tumor region[91]. This nanoparticle employed poly-L-lysine (PLL) to improve cellular uptake. The linker between PLL and PEG was neutravidin-iminobiotin bonds which are stable at pH = 8–12 but are easily decomposed at pH = 4–6 as a result of the lower affinity of the protonated iminobiotin to neutravidin, causing a cleavage of PEG shells. The exposing PLL layer enhanced the cellular uptake and facilitated retention of nanoparticles in tumor hypoxia region.

Except for electrostatic interactions as driving forces, other kinds of interactions are also applicable to facilitate layer-by-layer assemblies, including hydrogen bonding, covalent bonding, supramolecular inclusion, metal coordination and biospecific recognition. For example, Hammond *et al.* incorporated polymer micelles into layer-by-layer films utilizing hydrogen bonding[92]. This system employed the hydrogen bonding between PAA and a block polymer poly(ethylene oxide)-block-poly(ε-caprolactone) (PEO-*b*-PCL) as the linker of layers. Drugs were loaded on PEO-PCL and the layer-by-layer process was conducted repeatedly in acid condition. The layer-by-layer assembles were deposited in physiological environment to isolate free-standing layers and micelles by taking advantage of weak hydrogen bonding interaction.

Supramolecular Host-Guest Interaction

Since the Nobel Prize was granted to Lehn, Cram and Pedersen for their contribution to exploration of host-guest systems in 1987, host-guest based supramolecular systems have gained considerable attentions and made great devotion to the field of catalysis, separation, sensing, electronic devices, diseases therapeutics, *etc*[93]. In the host-guest chemistry, host molecules possess a spatial cavity which can accommodate guest molecules precisely on the basis of complementary shape and size, like a lock and key, providing a high selectivity. This accommodative interaction provides much possibility to establish self-assembled supramolecular system with structural complexity and programmable functions[94, 95]. Therefore, various host-guest systems have been developed over the years, and macrocyclic molecule-based such as cyclodextrins (CDs), cucurbit[n]urils (CB[n]s) and calix[n]arenes (CA[n]s) host-guest interactions have attracted increasing attentions in the biomedical field, owing to their good biocompatibility[96, 97].

In early studies, water-soluble macrocyclic molecules were directly used as the drug hosts to enhance the water solubility of drugs[98, 99]. By forming host-guest complexes, the encapsulated drugs can be protected from degradation in biological environment, and released sustainably from the cavity of macrocyclic molecules, achieving prolonged therapeutic effect. However, the application of this single host-guest inclusion complexes was restricted by their poor biosafety and therapeutic efficiency, which are unable to meet the clinical requirement[93]. Combined with advantages of nano-sized delivery systems, supramolecular host-guest recognition was employed to construct versatile drug delivery nano-systems for disease therapy with better efficiency and safety[100, 101]. This self-assembled method gives much flexibility to (1) design and control drug delivery systems with desirable sizes and morphology; (2) enhance drug solubility in aqueous; (3) deliver drug targetedly into specific sites; (4) internalize effectively into target cells[94]. To date, various types of self-assembled host-guest nano-systems have been developed in the forms of supramolecular nanoparticles, vesicles, and micelles[102].

Supramolecular nanoparticles induced by host-guest interaction

Supramolecular nanoparticles based on host-guest interaction are one of the most applicable vehicles in drug delivery, driven by the host-guest complexation between macrocyclic molecules and guest molecules[103]. During the self-assembly process of host-guest complexation, drugs can be capsulated inside the nanoparticles. For example, Zhao *et al.* developed a multifunctional supramolecular nanoparticles formed by the complexation of β-CD conjugated poly(acrylic acid) (PAA-CD), Ad conjugated PAA (PAA-Ad), and Ad conjugated PEG (PEG-Ad)[104]. The DOX was loaded during the self-assembly process. Folic acid was also conjugated on Ad to achieve selective drug delivery.

To maximize the drug efficiency, stimuli-responsive supramolecular nanoparticles were designed to release drugs when dissociation was triggered under various stimuli[105, 106]. Zhang *et al.* constructed a multifunctional supramolecular nanoparticle against cisplatin resistant cancer cells, in which the host molecule was Pt-CD, a platinum (IV) prodrug bridged β-CD dimer, and guest molecule was referred to as TPyP-Ad, a porphyrin photosensitizer with four adamantyl moieties[107]. The two components clustered with each other *via* the host-guest interaction and grew to a nano-scale particle, which had a higher cellular platinum uptake induced by the rise of reactive oxygen species (ROS) under the visible light irradiation than dark. Integrating the

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chemical drug with photodynamic therapy, this supramolecular host-guest nanoparticle has gained a synergistic enhancement of the anti-cancer efficacy.

Supramolecular micelles induced by host-guest interaction

Micelle is another important type of supramolecular self-assembly for drug delivery. The details of micelles used to deliver drugs for disease therapy have been discussed in the second part. Owing to the biocompatibility and stimuli-responsive degradability of host-guest molecules, a variety of micelles based on host-guest interaction were fabricated to deliver drugs in a smart manner[105, 106]. For example, Ji *et al.* reported a supramolecular micelle based on CB[8] complexation with methyl viologen-functionalized doxorubicin (MV-DOX) and naphthalene-terminated poly(ethylene glycol) (PEO-Np)[108]. CB[8] was used as a linker to connect DOX and PEO segment through the host-guest interaction with MV and naphthalene respectively, forming a ternary complex. The hydrophobicity of DOX induced the self-assembly of the ternary complexes into micelles. DOX was released *via* the acid-labile hydrazine bond conjugation with MV at endo-/lysosomal pH.

Supramolecular vesicles induced by host-guest interaction

Host-guest interactions have also been utilized to fabricate artificial vesicles as drug nano-carriers originating from polar/nonpolar interaction provided by amphiphilic surfactants[109]. A vesicle is typically derived from amphiphiles with different polar or hydrophilic head groups and hydrophobic tails. Owing to advantages of uniform size, ease of fabrication, and empty hollow cores for a large amount of drug storage, plenty of vesicles have been developed for drug delivery[110]. The host-guest complexation can provide a driving force for the vesicle formation as well as offer facile modifications on the external surface of vesicles. For the purpose of releasing drugs, stimuli-responsive groups were introduced into host-guest vesicles to accelerate disassembly[105, 106]. Responsive drug-delivery vesicles could greatly minimize side effects generated from burst release of drugs. For instance, Yan *et al.* reported a kind of novel Janus hyperbranched polymer (JHBP) vesicles driven by AZO/CD host-guest interactions[111]. A hydrophobic hyperbranched poly-(3-ethyl-3-oxetanemethanol) and a hydrophilic hyperbranched polyglycerol were modified with an azobenzene (AZO) group and a β-CD, respectively. The two blocks coupled together *via* AZO/CD host-guest interactions and disassembled reversibly upon irradiation of UV light due to the *trans*-to-*cis* isomerization of the AZO groups.

Other Self-assembly Nano-system in Disease Therapy

Self-assembled nano-therapeutic systems through other driving forces or manners are also evolved such as van der Waals force, coordinate bond, magnetic force, *etc*[112, 113]. Although the development of these systems has gained beneficial effects, they are not involved in mainstream of nano-therapeutics.

Recently, a novel approach containing interface-assembled polymer network initiated by *in situ* polymerization was proposed and developed in blossoming for protein and RNA therapeutic[114]. This novel approach firstly appeared in 2006, in which a single enzyme, horseradish peroxidase, was encapsulated in an assembled nanogel to enhance protein biocatalytic activity and stability[115]. Preparation of this nanogel contained a two-step procedure including surface acryloylation and *in situ* aqueous polymerization. The protein firstly reacted with acrylate molecules to attach polymerization site on the surface. Then *in situ* polymerization was initiated in aqueous solution, and monomers were aggregated around the surface of protein, crosslinking to assemble a thin polymer network around the polymer. According to this protocol, a plenty of protein and enzyme nanocapsules were developed for disease treatments. Advantages of this interface-assembly are emphasized on that: (1) the polymer shell stabilizes the protein against proteolysis and non-physiological environments and is thin enough for small molecular to permeate through; (2) the size of single protein nanocapsule is approximately 20 nm which is favorable for systemic circulation; (3) the properties of the nanocapsule including charge, degradability, hydrophibility, can be tuned by the choice of functional monomers and crosslinkers. Therefore, this interface-assembled nanocapsule has been widely used for protein therapy[3].

However, the acryloylation of protein will decrease the protein activity. Lu's group developed an *in situ* polymerization protocol based on non-covalent interaction to solve this problem. In their process, monomers and crosslinkers were adsorbed and enriched around the proteins spontaneously *via* electrostatic or hydrogen-bonding interactions and subsequently polymerized to form a cocoon-like nanocapsule[116–118]. This method realized that the intact protein was weaved in a polymeric network without modification, and greatly preserved the original activity of the protein.

In addition, protein nanocapsule will suffer the elimination by mononuclear phagocyte system. To prolong the circulation time of therapeutic proteins as well as minimize their immunogenicity, 2-methacryloyloxyethyl phosphorylcholine (MPC) was employed as the monomer of *in situ* polymerization owing to evasion of mononuclear phagocyte system (MPS). The resulting nanocapsule was coated with a zwitterionic polymer shell shielding serum protein adsorption under blood flow and prolonging half-life in blood circulation[119].

Nowadays, in order to maximize the protein efficiency, degradable polymer networks have been constructed to release the wrapped proteins. For example, Gu *et al.* designed a strategy to encapsulate the caspase-3 (CP3) protein in a degradable polymeric through utilization of a Asp-Glu-Val-Asp (DEVD) containing crosslinker[117]. DEVD peptide can be recognized and cleaved by CP3 from inside, realizing the disassembly of encapsulating shell. Similar to Gu's work, a series of degradable protein nanocapsules taking advantage of environmental responsive manner have been constructed for efficient intracellular delivery or tunable controlled release of protein. For example, Zhao *et al.* used *in situ* polymerization to encapsulate the recombinant maltose-binding protein fused apoptin (MBP-APO) with a disulfide bond (*S*-*S*) containing crosslinker which can be degraded when nanocapsules were exposed to the reducing environment in cytoplasm[120]. Tian *et al.* developed a protein

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capsule for controlled release of growth factor by using an alkaline-degradable cross-linker glycerol dimethacrylate (GDMA), which was gradually cleaved in base environment, leading to the disassembly of the polymer shells and the tunable release of the protein cargo[121].

Alternatively, siRNA can also be embedded into the nanocapsule. Liu *et al.* utilized this polymer shell to entrap miRNA (AS-miR-21) to enhance miRNA stability and effective intracellular delivery, suppressing the angiogenesis and achieving tumor retrogression in the cancer cells[122].

ADVANCED APPLICATION WITH SELF-ASSEMBLED NANO-CARRIERS IN THERAPY

The concept of self-assembled nanocarrier therapeutics can be traced back to the 1950s, and various types of self-assembled carrier systems have been developed in the following decades. In this part, we introduce a series of selected examples to highlight a number of advanced applications with self-assembled nano-carriers in therapy for cancers, metabolic disorders and infectious diseases.

Cancer Therapies

Cancer is one of the major causes of death worldwide. Although cancer therapies are developing, the treatment remains one of the most challenging problems[123–125]. Current traditional chemotherapeutic drugs (*e.g.*, doxorubicin, paclitaxel, platinum, *etc.*) and biomacromolecule drugs (*e.g.*, peptides, enzymes, antibodies, nucleic acids, *etc.*)[126, 127] are restricted during the cancer therapy due to their poor solubility or stability in physiological condition, short circulation half-life, lack of targeting capability (less than 5%)[128] and serious side effects to healthy tissues. Nanotechnology is anticipated to help us to solve the aforementioned problems. After several decades of developments, drug-delivery systems based on self-assembled nanoparticles have sparked a great promise[129–131]. Although the majority of self-assembled nanoparticles have encountered some unavoidable hurdles in the quest towards application for cancer treatments, they are not stranger to clinic. Compared with free therapeutic drugs, self-assembled nanoparticles with appropriate size (50–200 nm) and surface properties can selectively deliver various drugs to the cancerous tissues through passive or active tumor targeting, enhance tumour cell uptake and reduce the side-effects. Advanced applications with various self-assembled nanoparticles for drug delivery of both chemotherapeutic and biomacromolecule cargos in cancer therapy, as well as their merits and drawbacks, will be discussed in the following paragraphs.

Poly(ethylene glycol)-block-poly(ε-caprolactone) (PEG-*b*-PCL), a class of amphiphilic polyester copolymers, is widely used to encapsulate the anticancer drugs. It exhibits great biocompatibility, biodegradability and low cytotoxicity. Gao *et al.* reported a novel mixed-shell micelle (MSM), which was synthesized through the self-assembly of PEG-*b*-PCL and PAE-*b*-PCL, as drug nanocarrier loaded with doxorubicin (DOX) and demonstrated the improved anticancer effect in a tumor-bearing mice by prolonging blood circulation as well as enhancing cellular uptake (Fig. 1)[132]. Benefiting from the rational design with pH sensitive PAE segment in the shell,

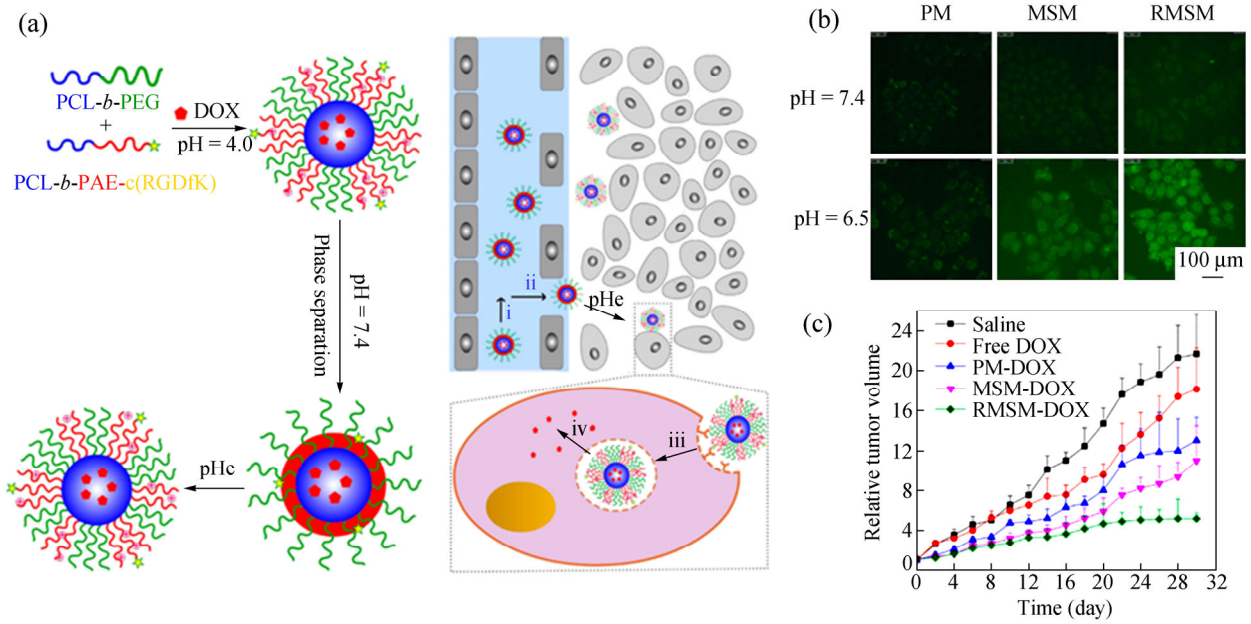

Fig. 1 Self-regulated multifunctional collaboration of targeted nanocarriers for enhanced tumor therapy: (a) Schematic illustration of c(RGDfK)-decorated, pH-responsive, mixed shell micelles loaded with DOX (RMSM-DOX), and the antitumor process of the RMSM-DOX after intravenous injection (RMSM-DOX possessed the properties of (i) prolonged blood circulation, (ii) increased tumor accumulation, (iii) enhanced cellular internalization attributed to the charge conversion and targeting effect of exposed c(RGDfK) group at tumor acidic microenvironment, and finally (iv) sufficient intracellular drug release.); (b) Cellular uptake of FITC-labeled PM, MSM, and RMSM on HepG2 cells observed by inverted fluorescent microscopy (Cells were co-incubated with micelles for 2 h at pH = 7.4 and 6.5.); (c) *In vivo* antitumor inhibition of free DOX, PM-DOX, MSM-DOX, and RMSM-DOX (Reprinted with permission from Ref. [132]; Copyright (2014) American Chemical Society)

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the mixed-shell micelles exhibited significantly prolonged plasma half-life at pH = 7.4, but were internalized in acidic tumor microenvironment, owing to the rapid surface conversion to positively charge at pH = 6.5. Furthermore, the active-targeting ligand c(RGDfK) conjugated to the hydrophobic PAE segment was also exposed, exhibiting synergistic effects to facilitate cellular internalization[133].

However, a primary drawback of self-assembled polymeric micelles based on hydrophobic interactions is their relative instability in blood, leading to rapid dissociation and burst release *in vivo*. To address this issue, innovative approaches have been used to engineer the core of assembled polymeric micelles: (1) introduce hydrogen-bond interaction in the core; (2) increase the hydrophobicity of the core by grafting aromatic or cholesterol groups[134, 135]; (3) improve electrostatic interaction by introducing different charged groups in the core[136, 137]; (4) link the drugs with covalent bond to the backbone.

Gao *et al.* developed a smart self-assembled polyion mixed shell micelles (MSMs) based on electrostatic interaction between polycationic and polyanionic segments and hydrogen-bond interactions to remarkably decrease deposition in liver and spleen and prolong the blood circulation by increasing their stability (Fig. 2)[136]. They fabricated a series of mixed shell micelles with different hydrophilic/hydrophobic ratios in the shell through varying the ratios of the block copolymers, changing the size and surface charge of the MSMs. The biodistribution was investigated systematically through tracking the ^{125}I-labeled MSMs *in vivo*, and the MSMs were observed with more than 3 times lower accumulation in liver and spleen and 6 times higher concentration in blood at 1 h after intravenous injection than single PEGylated micelles. Cheng *et al.* designed a type of self-assembled mixed-shell micelle (MSM) with DOX-conjugated block polymers (*i.e.*, poly(lysine-colysine-*cis*-aconityl-Doxorubicin)) with an acid-cleavable linker as the hydrophobic core and PAE/PEG as the mixed shell based on the rapid and reversible protonation/ deprotonation of PAE to increase relative stability, which addresses the dilemma between prolonging circulation time and enhancing cellular uptake, providing a promising drug delivery platform for cancer therapy (Fig. 3)[134].

Wang *et al.* reported a dual pH-sensitive micelle system, which was precisely constructed through the self-assembly of block polymers, driven by the hydrophobic interaction between DOX moieties, and hydrogen-bond interaction between polymers (Figs. 4a and 4b)[35]. They attached DOX to the polymer (*i.e.*, poly(ethylene glycol)-*b*-poly(allyl ethylene phosphate)-cysteamine) by an acid-labile hydrazone bond, which showed endo/lysosomal (pH = 4.0–6.0) pH-sensitive DOX release. Meanwhile, the 2,3-dimethyl maleicanhydride (DMMA) was conjugated to the amino in polymer by amide bond, which could be cleaved under slightly acidic conditions, leading to the reverse of its surface charge from negative to positive at tumor extracellular pH (~6.5) to facilitate cell internalization. This dual pH-sensitive micelle system has shown enhanced cytotoxicity in drug-resistant cancer stem cells. Subsequently, an acid-sensitive copolymer based on a functionalized maleic anhydride and PEG/PCL was developed, which could induce PEG detachment at tumor sites, and be used for tumor-targeted systemic delivery of biomacromolecule drugs, such as siRNA (Figs. 4c–4e)[138]. Using this polymer, a drug delivery system (D_m-NP) was formed by utilizing hydrophobic interaction and electrostatic interaction between siRNA and the polymers containing cationic arginines (R9). Meanwhile, the R9 was a

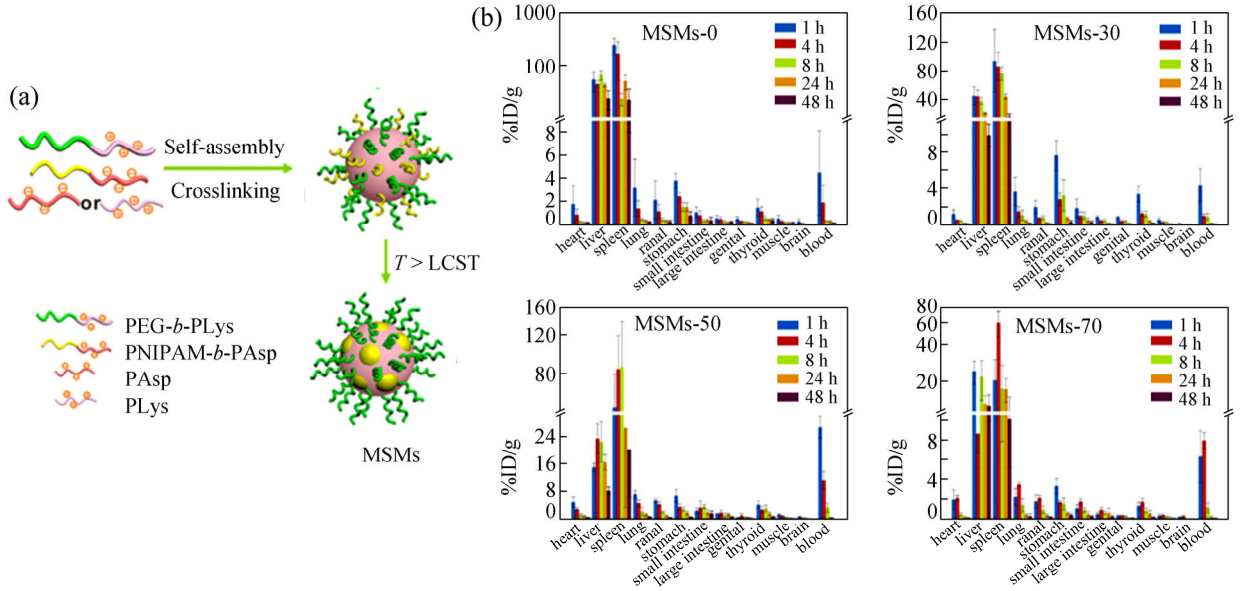

Fig. 2 *In vivo* biodistribution of mixed shell micelles with tunable hydrophilic/hydrophobic surface: (a) Schematic illustration of the formation of MSMs with microphase separated surface; (b) *In vivo* biodistribution of four different MSMs labeled with ^{125}I (Tissues were harvested and weighed at five various time points (1, 4, 8, 24, and 48 h) after initial inject *via* the tail vein of BALB/c mice with MSMs of MSMs-0, MSMs-30, MSMs-50, and MSMs-70, respectively (5 mg MSMs/kg mice body weight; data are expressed as percent injected dose per gram (%ID/g) ± standard deviation, n = 5).) (Reprinted with permission from Ref. [136]; Copyright (2013) American Chemical Society)

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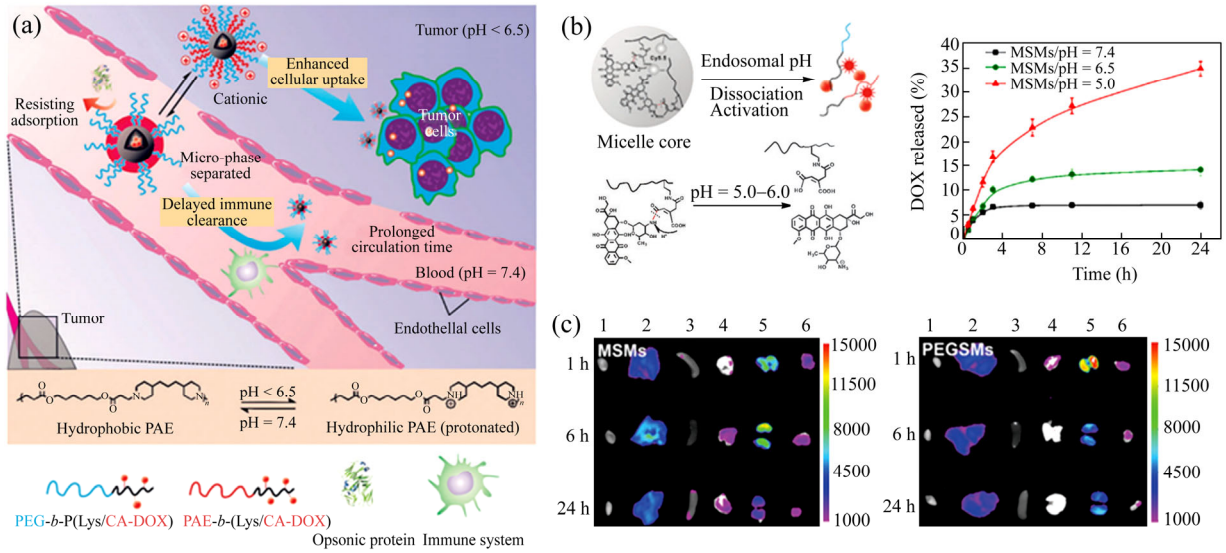

Fig. 3 A surface-adaptive nanocarrier to prolong circulation time and enhance cellular uptake: (a) Surface-adaptive mixed-shell micelles (MSMs) self-assembled from two polymer-drug conjugates and an adaptive surface mechanism to prolong circulation time and enhance cellular uptake based on the pH-responsive properties of PAE; (b) Illustration of MSM dissociation and *in vitro* release profiles of DOX from MSM under different pH conditions; (c) *Ex vivo* fluorescence imaging of the tumor and normal tissues harvested from the MDA-HepG2 tumor-bearing nude mice at 1, 6 and 24 h after injecting MSMs and PEGSMs (The numeric label for each organ is as follows: 1, heart; 2, liver; 3, spleen; 4, lung; 5, kidney; and 6, tumor.) (Reprinted with permission from Ref. [134]; Copyright (2015) The Royal Society of Chemistry)

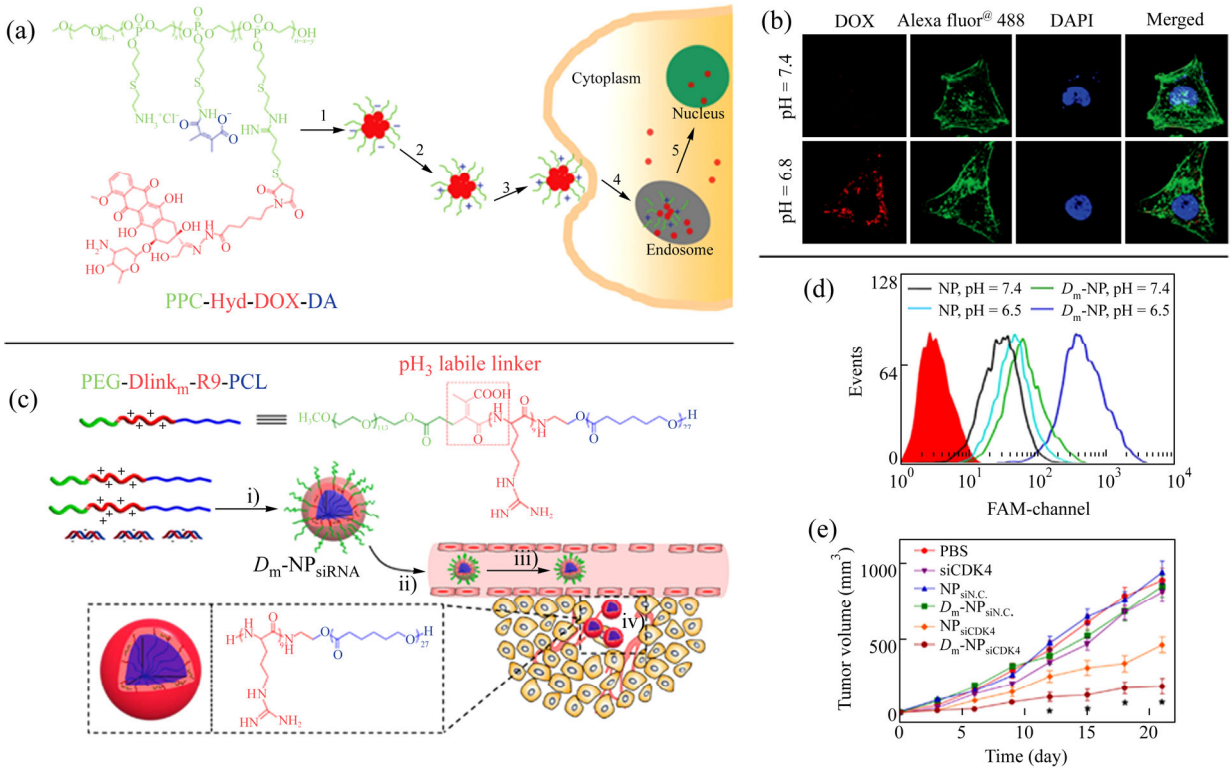

Fig. 4 Tumor acidity-sensitive polymeric vector for active targeted delivery: (a) Chemical structure of the dual pH-responsive polymer doxorubicin (DOX) conjugate (PPC-Hyd-DOX-DA) and illustration of its pH triggered cellular internalization and intracellular drug release; (b) Cellular uptake of PPC-Hyd-DOX-DA NPs (red) at pH = 6.8 or 7.4 after incubation with MDA-MB-231 cells for 1 h; (DAPI (blue) and Alexa Fluor488 phalloidin (green) were used to stain cell nuclei and F-actin, respectively.); (c) Polymer-based nanoparticles and their change in response to tumor acidity; (d) Flow cytometry analysis of A549 cells after incubation with FAM-siRNA loaded NP or D_m-NP at pH = 7.4 or 6.5 for 2 h (The dose of FAM-siRNA was 200 nmol/L in the cell culture.); (e) Tumor growth inhibition in A549 tumor xenograft-bearing nude mice after different treatments (n = 5) (The dose of siRNA was 40 μg per mouse per injection, $^*P < 0.05$ when compared with NP$_{siCDK4}$.) (Reprinted with permission from Ref. [35]; Copyright (2011) American Chemical Society; Ref. [138]; Copyright (2015) American Chemical Society)

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cell-penetration peptide, which was exposed upon the removal of PEG and further enhanced cellular uptake. Thus, systemic administration of D_m-NP_{siCDK4} exhibited superior gene silencing efficiency and tumor inhibition activity with fewer side effects in non-small cell lung cancer.

Polymers having protonated amines at physiological pH also open a way to incorporate anionic molecules (*e.g.*, nucleic acids[139, 140], proteins[141], polysaccharides *etc*[142].) into the nanoparticles *via* electrostatic interaction. Recently, Guan *et al.* developed an ultrasensitive pH triggered charge/size dual-rebound gene delivery nanoparticles (NPs) for cancer treatment (Fig. 5)[139]. Firstly, the negatively charged therapeutic gene, such as DNA, was mixed with PEI and PLG based on electrostatic interaction to form the gene loaded NPs, then the NPs were further tightened by PEG which had aldehyde groups at both of terminals *via* Schiff base reaction with amines. Resulting from the reduced surface positive charges and tightened complex particles by PEG linkers, the gene delivery system aforementioned could lead to improved stability, prolonged circulation and decreased cytotoxicity. However, when the PEG was peeled under slightly acidic conditions, the NPs were rebounded to higher positive potential and bigger size which could accelerate cellular uptake process. Subsequently, an antiangiogenesis therapeutic gene was carried for the treatment of CT26 tumors in mice, achieving superior antitumor efficacy. Tang *et al.* described a biomimetic protein delivery system which was degradable by furin, a ubiquitous intracellular proprotein endoprotease in humans that could efficiently cleave precursor proteins at the paired basic amino acid processing sites, to release the encapsulated therapeutic protein, apoptotic protease caspase-3 (CP3) (Fig. 6)[143]. The proteins were encapsulated in a nanosized layer prepared with neutral and positively charged monomers and bisacrylated peptide cross-linkers, such as RX(K/R)R↓ (R: arginine; K: lysine, X: any amino acid; ↓: the cleavage site), *via in situ* polymerization followed by electrostatic assembly that could be specifically recognized and cleaved by furin. *In vitro* studies demonstrated successful intracellular delivery of anticancer CP3 to HeLa cells, both nuclear and cytosolic proteins, and then cell apoptosis was remarkably observed owing to the CP3 release. This platform might also be applicable to intracellular delivery of other biological therapeutics, including siRNA and plasmid DNA.

Liu *et al.* introduced a convenient type of protein delivery system using self-assembled supramolecular nanoparticles (SNPs), which was based on electrostatic interaction and host-guest recognition, capable of highly efficient transduction of intact (unmodified) transcription factors (TFs) when incubated with HeLa cells (Fig. 7)[144]. They prepared an anionic TF·DNA complex composed of a DNA plasmid with a matching recognition sequence and a TF, which could be subsequently encapsulated into SNPs by cationic cyclodextrin-polyetherimide (CD-PEI), and then SNPs were modified with different functional groups (*i.e.*, Ad-PEG, Ad-PEG-RGD, and Ad-PEG-TAT) to enhance the uptake in target cells. The results provided us with an example for the future development of SNPs as promising protein delivery carriers for cancer therapy.

Self-assembled liposomes were also evaluated as one of the most established nano-carriers in 1970s. Currently, many kinds of cancer drugs including small hydrophobic drugs and biomacromolecule drugs, have been applied to the liposome-based systems both in mice and human clinical trials[145]. For instance, liposome doxorubicin (Doxil®) and liposomal paclitaxel (LEP-ETU, EndoTAG®-1, Lipusu®) are approved by the Food and Drug Administration (FDA), and widely used to treat metastatic breast cancer, ovarian cancer, non-small cell lung carcinoma, melanoma, and Kaposi's sarcoma while protecting patients from the cardiotoxicity of the unencapsulated drug[146–150]. Biomacromolecule drugs, such as L-asparaginase, have been entrapped

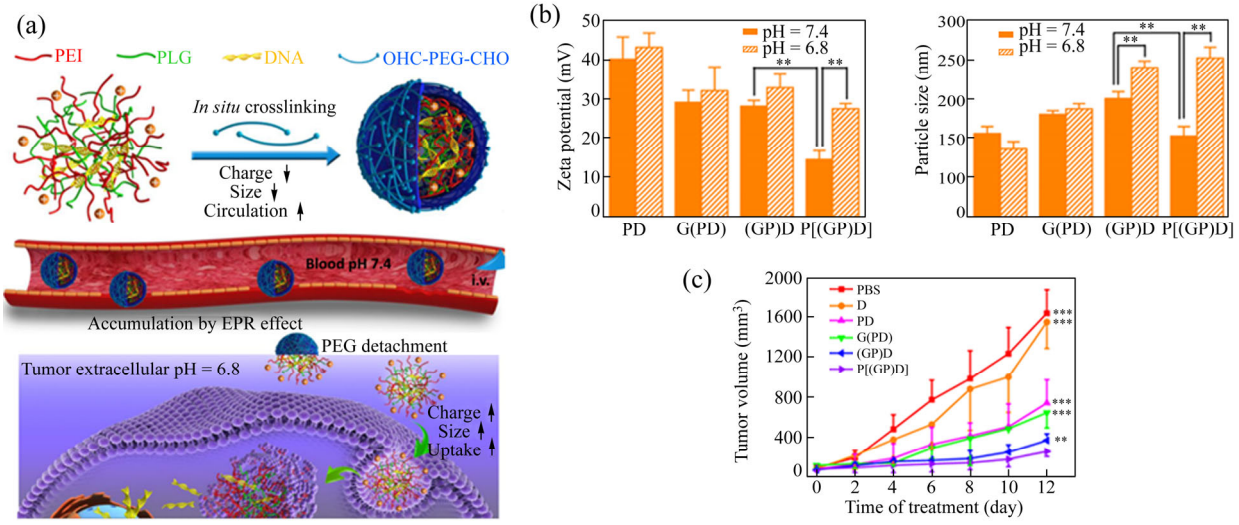

Fig. 5 Ultrasensitive pH triggered charge/size dual-rebound gene delivery: (a) Schematic of the ultrasensitive pH triggered charge/size dual-rebound gene delivery system; (b) Zeta potential and particle size of the NPs; (c) Tumor volume changes of the mice administered with PBS, D, PD, G(PD), (GP)D, and P[(GP)D] by intravenous injection (NPs were prepared by mixing DNA, PEI, PLG or PEG aqueous solutions with equal volume in different orders.) (Reprinted with permission from Ref. [139]; Copyright (2016) American Chemical Society)

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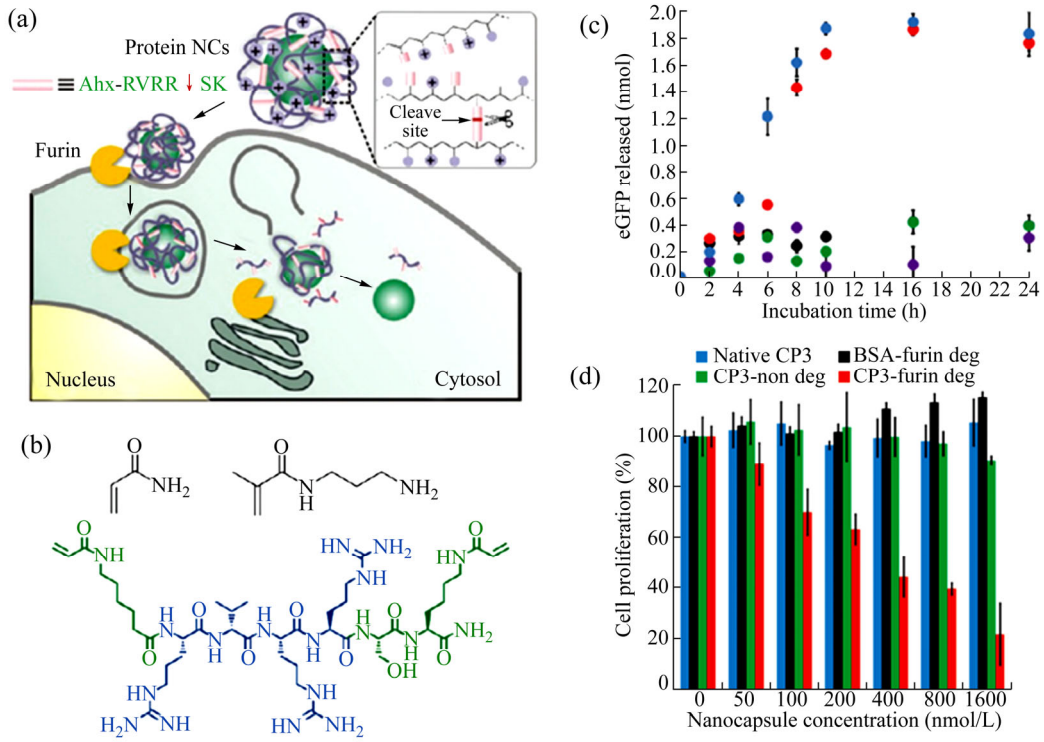

Fig. 6 Endoprotease-mediated intracellular protein delivery: (a) Monomers and furin-degradable crosslinkers (CLs) polymerized to create a degradable polymeric matrix around protein (Nanocapsules (NCs) degrade intracellularly and protein releases upon proteolysis of the CLs by furin.); (b) Structure of monomers, acrylamide and *N*-(3-aminopropyl) methacrylamide, and synthesized furin-degradable CL used to form NCs; (c) eGFP release by 2.5 nmol NCs for 10 h (Black solid circle: Furin-degradable NCs; Furin-degradable NCs with 1 U (red solid circle) and 4 U (blue solid circle) furin; Green solid circle: Furin-degradable NCs with 1 U furin and dec-RVKR-cmk; purple solid circle: NCs with nondegradable CLs. The data represent averages with error bars from three independent experiments.); (d) Cell death profiles of HeLa cells treated with various cross-linked NCs/protein for 24 h before performing the MTS assay for quantification of cell proliferation (Reprinted with permission from Ref. [143]; Copyright (2011) American Chemical Society)

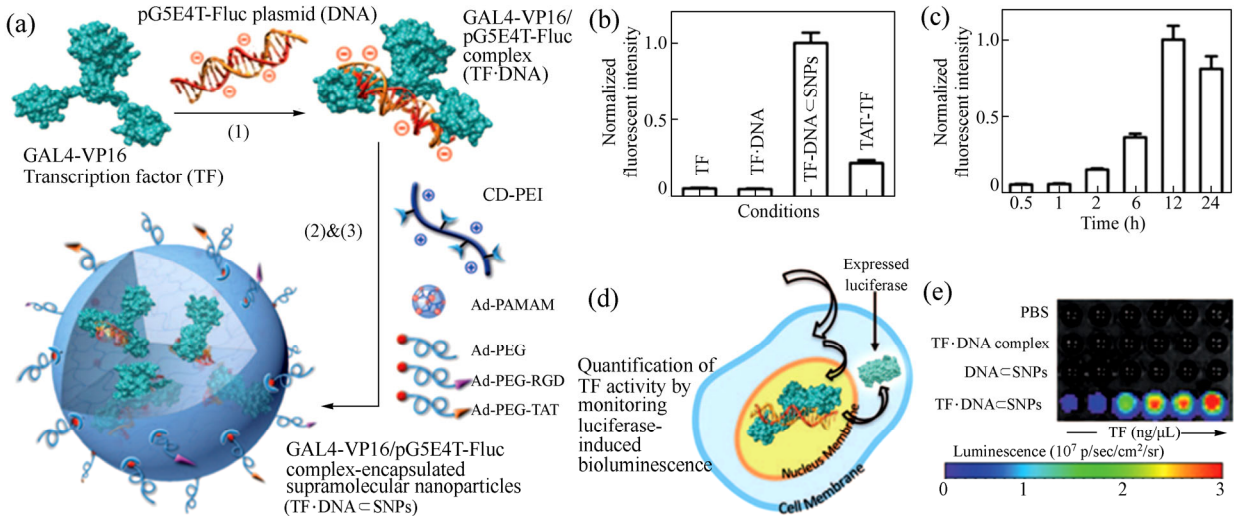

Fig. 7 Delivery of intact transcription factor by using self-assembled supramolecular nanoparticles: (a) Schematic representation of the self-assembly approach for the preparation of transcription factor-incorporated supramolecular nanoparticles (TF·DNA⊂SNPs) (Three types of molecular recognition mechanisms: 1) specific binding between GAL4-VP16 (TF) and pG5E4T-Fluc plasmid (DNA) for formation of an anionic TF·DNA complex, 2) the Ad/CD-based molecular recognition for generation of SNP vectors with cationic PEI/PAMAM hydrogel cores, and 3) electrostatic interactions that facilitate incorporation of anionic TF·DNA into SNPs, were harnessed for the self-assembly of TF·DNA⊂SNPs by simply mixing TF·DNA with five functional molecular building blocks: CD-PEI, Ad-PAMAM, Ad-PEG, Ad-PEG-RGD, and Ad-PEG-TAT.); (b) Quantification studies on the delivery performance of TF·DNA⊂SNPs; (c) Time dependent uptake studies of TF·DNA⊂SNPs; (d) Bioluminescence study on TF·DNA⊂SNPs-treated cells (The activity of GAL4-VP16 can be reflected in the bioluminescence intensity as a result of luciferase expression.); (e) Bioluminescence imaging of TF·DNA⊂SNPs-treated cells along with the controlled experiments based on TF·DNA complex and DNA⊂SNPs (Reprinted with permission from Ref. [144]; Copyright (2011) Wiley-VCH)

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within the aqueous core of the liposomes, providing a longer circulating time and weaker acute toxicity *in vivo* compared with the free enzyme[151]. Moreover, several progresses have also been achieved *via* liposomal vectors in gene therapy to increase the transfection efficiencies[152–155].

In recent years, new generation liposomes are smarter than before on preventing nonspecific interactions and prolonging circulation time, while enhancing tumor accumulation by targeting ligands (*e.g.*, peptide, monoclonal antibody, *etc.*). Zhu *et al.* reported a multifunctional drug delivery system with "smart" surface based on liposomes responding to the up-regulated matrix metalloprotease 2 (MMP2) in the tumor microenvironment, improving cancer cell-specific delivery of loaded drugs (Fig. 8)[156]. The merits of the liposome included (1) the hydrophilic and flexible PEG chains prolonging the circulation time; (2) a mAb 2C5, which had been modified to the PEG, allowing for the specific targeting of tumor cells; (3) a MMP 2-sensitive bond between long PEG chains and lipid that underwent cleavage in the tumor for the removal of PEG chains; (4) the cell-penetrating peptide (TATp) becoming exposed and enhancing intracellular delivery. Experimental results showed that the liposomes could reach a precise and effective tumor targeting and intracellular delivery. Gu *et al.* developed a liposome-based co-delivery platform containing a fusogenic liposome encapsulating ATP-responsive elements and a liposome encapsulating ATP for drug release mediated by the liposomal fusion in acidic compartments (*e.g.*, endosomes or lysosomes) (Fig. 9)[54]. The ATP-responsive elements were composed of DNA scaffold and doxorubicin (DOX). Interestingly, the release of the intercalated DOX could be triggered by a conformational change in the presence of ATP (1–10 mmol/L), and anticancer efficacy was obviously enhanced both *in vitro* and *in vivo* compared with that without ATP-liposome (ATP-L).

Metabolic Disorders

Over the last few decades, a fleetly increasing number of studies have focused on a cluster of chronic metabolic disorders, especially dementia mellitus and neurodegeneration, which have been serious threats for the health of all populations with significant morbidity and mortality. This section highlights several recent works aiming at the applications of self-assembled nanoparticles in treating metabolic disorders.

Diabetes mellitus is a type of chronic diseases characterized by hyperglycemia due to the deficiency in insulin secretion or insulin action. Namely, the diabetic is unable to regulate the concentration of blood glucose within normal physiological level, leading to many long-term complications, including cardiovascular disease, atherosclerosis, nephropathy, retinopathy, *etc*[157–160]. Thus, it is important to develop suitable treatments for diabetes mellitus, such as injection of insulin[161, 162]. However, existing medical therapies of insulin-dependent diabetes mellitus still depend on the self-injection of insulin, which hardly satisfied either the necessity for precise glycemic control or patient compliance resulting from frequent injection[163]. For avoiding the great mental and physical pains

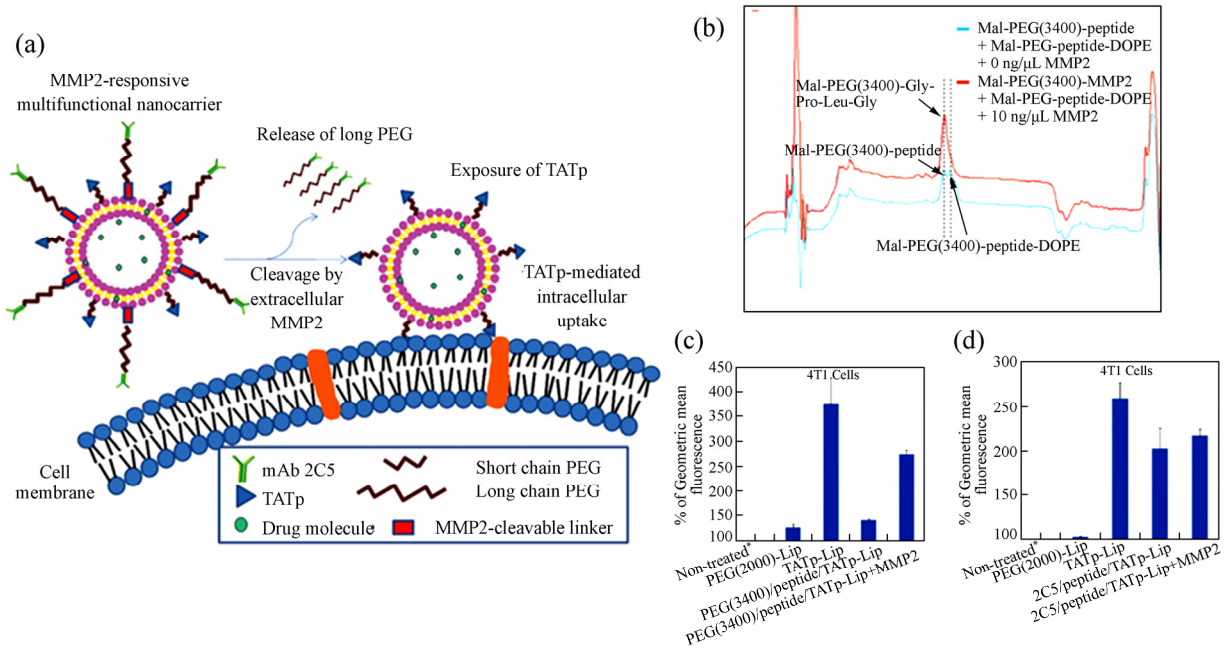

Fig. 8 Enzyme-responsive multifunctional liposomal nanocarrier for enhanced tumor targeting: (a) MMP2-responsive multifunctional liposomal nanocarrier and its drug delivery strategy (The multifunctional liposomal nano-carriers are retained in the tumor site due to the EPR effect and the active targeting effect by the anticancer mAb 2C5. The up-regulated MMP2 in the tumor microenvironment cleaves the MMP2-sensitive linker and removes the protective long-chain PEG, resulting in the exposure of TATp for the enhanced cellular internalization.); (b) Cleavage assays of the MMP2-cleavable peptide, which is treated with the active human MMP2 at 0 and 10 ng/μL, in HBS at 37 °C for 24 h (The reactions were followed using both RP-HPLC.); (c, d) FACS analysis of the interaction of Rh-PE-labeled MMP2-responsive multifunctional liposomal nanocarrier with 4T1 cells (Reprinted with permission from Ref. [156]; Copyright (2012) American Chemical Society)

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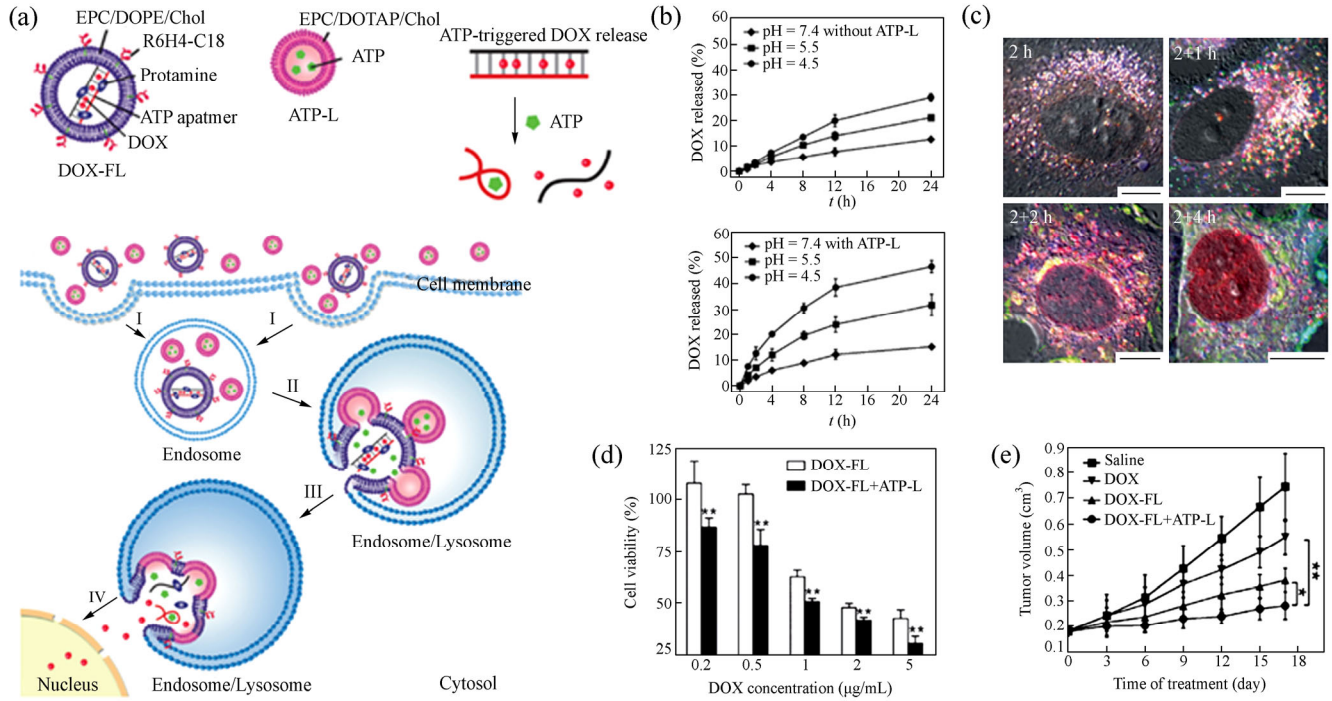

Fig. 9 Enhanced anticancer efficacy by ATP-mediated liposomal drug delivery: (a) Main components of DOX-FL and ATP-L (DOX-FL have an ATP-responsive protein-DNA complex core with DOX and a pH-sensitive CPP-modified fusogenic liposomal shell.), and the mechanism of ATP-triggered release of DOX through the structural transformation from the duplex to the aptamer/ATP complex); (b) *In vitro* release profiles of DOX from DOX-FL without and with ATP-L at different pH values (Data points represent mean ± SD (n = 3)); (c) CLSM images of MCF-7 cells after incubation with DOX-FL and NBD-ATP-L for different time (The cells were incubated with a mixture of DOX-FL and NBD-ATP-L for 2 h, and subsequently incubated with fresh culture medium for an additional 1, 2, or 4 h after removal of the excess liposomes. Late endosomes and lysosomes were stained by LysoTracker Blue. Red: DOX; green: NBD; blue: endolysosomes; yellow: colocalization of red and green pixels; magenta: colocalization of red and blue pixels; white: colocalization of red, green, and blue pixels. Scale bars are 10 μm.); (d) *In vitro* cytotoxicity of co-delivery of DOX-FL and ATP-L toward MCF-7 cells (Data points represent mean ± SD (n = 6). $^{**}P < 0.01$); (e) Tumor growth curves of the tumor-bearing mice after intratumoral injection with different DOX formulations (Reprinted with permission from Ref. [54]; Copyright (2014) Wiley-VCH)

caused by aforesaid problems, Wang *et al.* reported a convenient and effective method to fabricate a PBA-based block copolymer poly(ethylene glycol)-block-poly(acrylic acid-*co*-acrylamidophenylboronic acid) (PEG-*b*-P(AA-*co*-AAPBA)) that could respond to glucose at physiological conditions for insulin delivery and controlled release (Fig. 10)[164]. Modifying the AA segments to transform into AAPBA segments led to an amphiphilic block copolymer, which could self-assemble into core-shell micelles but dissociate in response to glucose at suitable concentration in neutral pH. The insulin was loaded *via* hydrophobic interaction during self-assembly, and could be released at a faster rate in the solution with higher concentration of glucose. Experimental data indicated that interaction between carboxyl and PBA groups induced the transform of PBA from trigonal planar to tetrahedral form, resulting in the decrease of apparent pK_a and glucose-responsiveness[165].

Liu *et al.* reported a phenylboronic acid (PBA)-functionalized glucose-responsive complex polymeric micelle (CPM) to control the blood glucose concentration *via* insulin delivery (Fig. 11)[166]. The CPM was synthesized containing two types of diblock copolymers, poly(ethylene glycol)-*b*-poly(aspartic acid-*co*-aspartamidophenylboronic acid) (PEG-*b*-P(Asp-*co*-AspPBA)) and poly(*N*-isopropylacrylamide)-*b*-poly(aspartic acid-*co*-aspartamido-phenylboronic acid) (PNIPAM-*b*-P(Asp-*co*-AspPBA)). When the weight ratio between PNIPAM and PEG was 6/4, the CPM exhibited a sensitive reversible swelling in response to the changes in glucose concentration, resulting from the repeated on-off release of insulin regulated by glucose level. It would be useful to mention that this CPM could also effectively protect the encapsulated insulin against proteolytic and hydrolytic degradation, thus improve the delivery efficiency.

Alzheimer's disease (AD) is acknowledged as a kind of irreversible neurodegenerative disorder, which is the primary cause of dementia in elder people and patients with Down syndrome at the age more than 50 worldwide[167]. According to statistics, one out of every eighty individuals may be expected to suffer from AD in 2050. AD can increase the risk including the progressive loss of mental, behavioral, functional decline and the ability to learn[168, 169]. Therefore, developing pharmacological treatments for AD is much imminent[170]. Pathologically, the AD is characterized by large numbers of intracellular neurofibrillary tangles and extracellular senile plaques consisting of β-amyloid (Aβ) protein deposits surrounded by neurons in brain tissue, in addition to neuronal cell loss[171–173]. According to the amyloid hypothesis, deposition of Aβ by misfolding in brain is the main influence leading to AD pathogenesis, resulting from

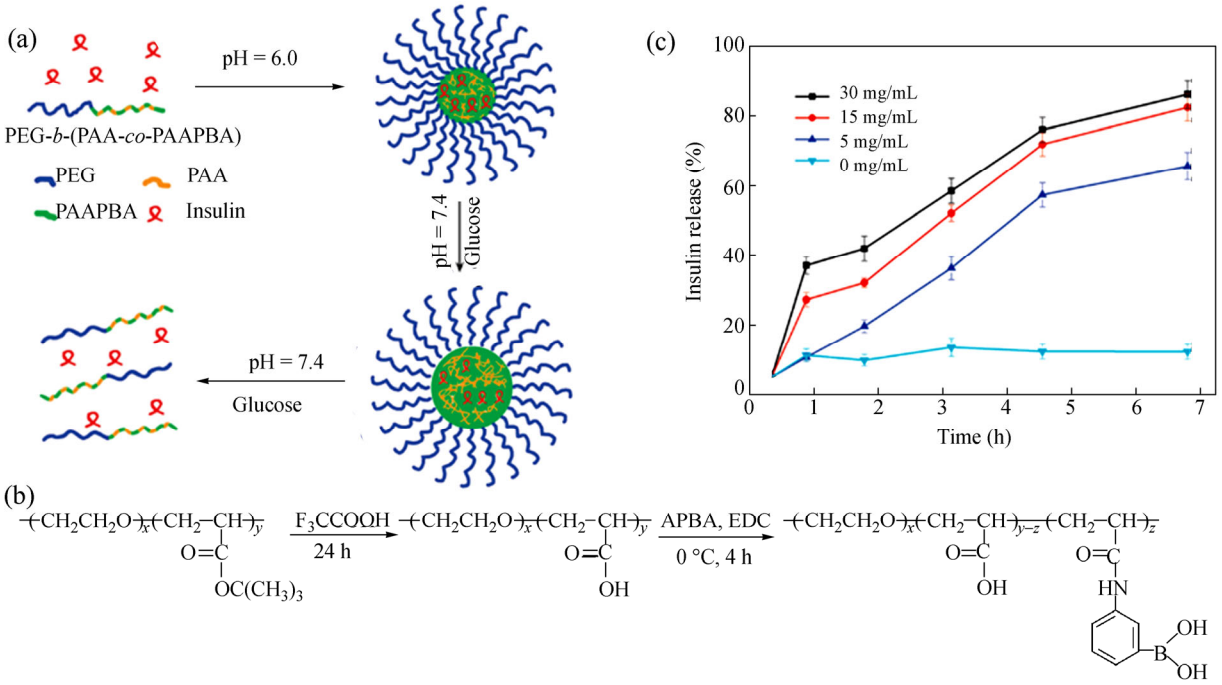

Fig. 10 Glucose-responsive micelles and the controlled release of insulin: (a) Schematic illustration of the formation, swelling, and disaggregation of insulin-loaded micelle and release of insulin from the micelle according to glucose responses; (b) Synthesis of PEG-*b*-(PAA-*co*-PAAPBA); (c) Insulin release from insulin-loaded micelles as a function of time in different glucose concentration PBS (pH = 7.4, 0.01 mol/L), c_{NaCl} = 6 mg/mL at 37 °C (All of the micelle solutions had the same polymer concentration of 0.60 mg/mL, and the insulin loading capacity was 29%.) (Reprinted with permission from Ref. [164]; Copyright (2009) American Chemical Society)

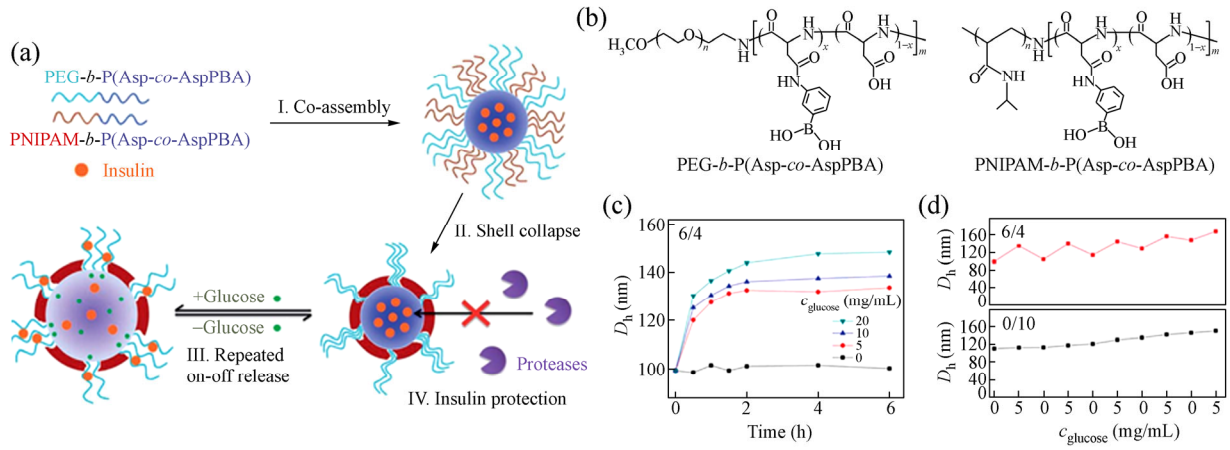

Fig. 11 A glucose-responsive complex polymeric micelle enabling repeated on-off release and insulin protection: (a) Schematic illustration of glucose-responsive complex polymeric micelle (CPM) self-assembled from two diblock copolymers for repeated on-off release and insulin protection under physiological conditions; (b) Chemical structures of PEG-*b*-P(Asp-*co*-AspPBA) and PNIPAM-*b*-P(Asp-*co*-AspPBA); (c) Reversible glucose-responsive swelling/recovery of CPMs exhibited by time-dependent D_h of the 6/4 CPMs under various glucose concentrations; (d) Reversible swelling/recovery of the CPMs in response to external stepwise glucose treatment every 1 h (Reprinted with permission from Ref. [166]; Copyright (2013) The Royal Society of Chemistry)

imbalance between Aβ production and Aβ clearance[174, 175].

Molecular chaperones[176], a class of essential proteins in the human body, play an irreplaceable role in controlling undesired protein misfolding and maintaining the intricate homeostasis of protein metabolism *in vivo*, also as an ideal candidate for AD treatment[177–181]. Huang *et al.* reported a novel artificial chaperone consisting of mixed-shell polymeric micelles (MSPMs) through hydrophobic interaction to maintain Aβ homeostasis and reduce neurotoxicity (Fig. 12)[178]. The MSPMs were obtained by the self-assembly of two amphiphilic diblock copolymers, poly(ε-caprolactone)-block-poly(ethylene oxide) (PCL-*b*-PEG) and poly(ε-caprolactone)-block-poly(*N*-isopropylacrylamide) (PCL-*b*-PNIPAM) in an aqueous solution. The hydrophobic domains on the surface act as cavities which interact with hydrophobic Aβ monomers and their oligomeric aggregates, while the hydrophilic PEG chains provide a protective layer to prevent the MSPMs from aggregation after absorbing Aβs.

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The results proved that the MSPMs with appropriate weight ratio of PNIPAM and PEG (PCL-*b*-PEG/PCL-*b*-PNIPAM = 3/7) could serve as an excellent suppressor of AD and show enhanced therapeutic effects in PC12 cells.

However, the MSPMs aforementioned could not disaggregate the fibrils and showed weak treatment effect if fibrils had been formed. Previous studies had suggested that the KLVFF sequence (residues 16–20 of Aβ)[182] could specially arrest full-length Aβ monomers and its aggregates *in vivo* due to the strong affinity with Aβ, and disaggregate fibrils into fragments[183–185]. Combining KLVFF peptide and self-assembly chaperone, Qu *et al.* reported a highly efficient platform to achieve the synergy between Aβ fibrils disaggregation and reducing Aβ-mediated neurotoxicity (Fig. 13)[185]. They modified KLVFF sequence onto the classical MSPMs, which consisted of poly(ε-caprolactone)-block-poly(β-amino ester) (PCL-*b*-PAE) and poly(ε-caprolactone)-block-poly(ethylene oxide) (PCL-*b*-PEG), to make sure the peptide interact with hydrophobic Aβ monomers. After the KLVFF peptides disaggregated the fibrils into fragments, the hydrophobic domains on the surface of the self-assemblies could promptly bind them in aqueous solution, leading to reduction of consequent toxicity. Besides disaggregating the fresh fibrils, the MSPMs could also assist protease in degrading tangled fibrils for maintaining the healthy proteostasis.

Additionally, metabolic acidosis caused by acute alcohol intoxication (a clinically harmful condition that follows the ingestion of a large amount of alcohol), which may trigger cardiovascular diseases, respiratory paralysis or gastrointestinal disease, has recently gained the increasing attentions[186–188]. Once has entered into organism, 90% percent of alcohol is oxidized by alcohol dehydrogenase (ADH) to acetaldehyde in the liver, which is subsequently converted to acetate by acetaldehyde dehydrogenase (ALDH), and finally metabolized to CO_2 and H_2O[189–191]. In this procedure, alcohol overdose may lead to the overproduction of reactive acetaldehyde and increase intracellular NADH/NAD+ ratio; meanwhile the acetyl coenzyme A (acetyl-CoA) cannot effectively participate in the tricarboxylic acid cycle in mitochondrion which can lead to excessive production of β-hydroxybutyric acid (β-HB) and the accelerated hydrolysis of fats. Thus, a therapeutic agent that is able to actively accelerate ethanol excretion and reduce blood alcohol concentration is highly demanded for the management of alcohol intoxication. For example, metadoxine capsules are a kind of useful drugs in the treatment for acute alcohol intoxication through accelerating ethanol excretion[192]. An alternative enzyme therapeutic potentially applicable to alcohol detoxification is alcohol oxidase (AOx). Based on this enzyme, Liu *et al.* found that two or three enzymes with complementary functions, such as alcohol oxidase (AOx) and catalase (Cat), could be assembled *via* the specific interaction with DNA-inhibitor scaffolds and encapsulated within a thin polymer shell to form robust enzyme nanocomplexes (Fig. 14)[193]. The enzyme nanocomplexes containing AOx and Cat were characterized with enhanced stability and improved efficiency, as well as complementary and synergic functions compared with free enzymes, and could reduce blood alcohol levels apparently in intoxicated mice.

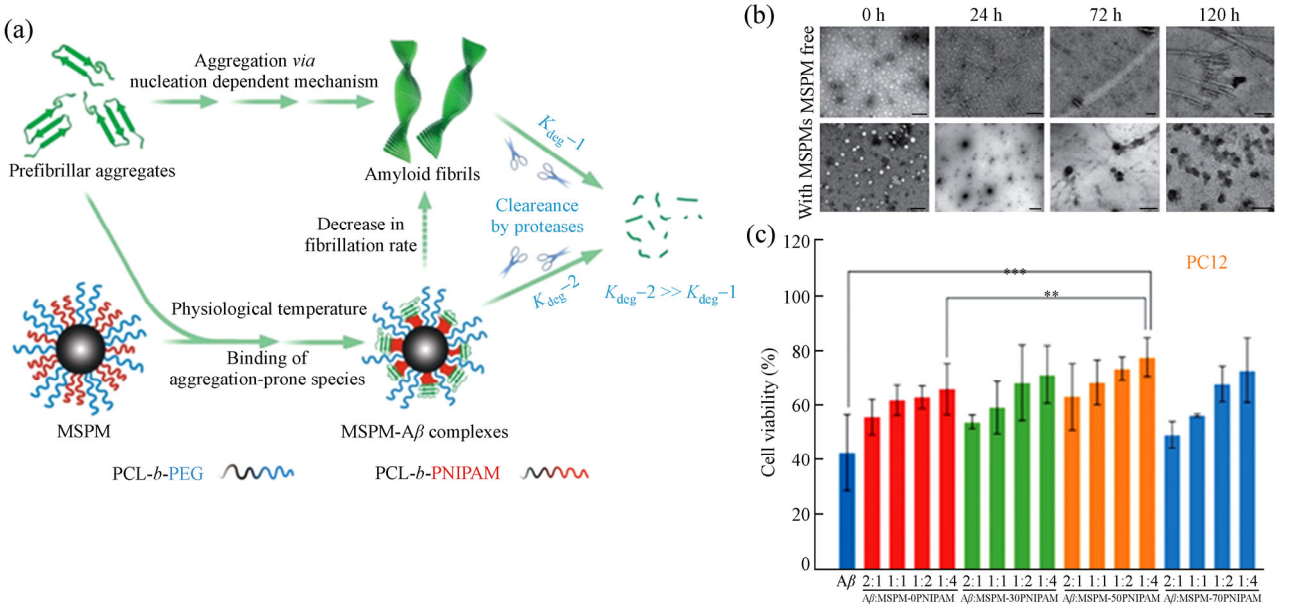

Fig. 12 Maintenance of Aβ peptide homeostasis by artificial chaperones based on mixed-shell polymeric micelles: (a) Illustration of the degradation of amyloid fibrils and MSPMs-Aβ complexes; (b) TEM images of Aβ incubated with and without MSPMs at different time points (37 °C) of the fibrillation process (The PCL-*b*-PEG/PCL-*b*-PNIPAM ratio in the MSPMs was 3/7 (*W*/*W*). [Aβ] = 20 μmol/L, [MSPMs] = 0.4 mg/mL. Buffer: 10 mmol/L PBS, pH = 7.4. scale bar: 200 nm); (c) PC12 cells viability measured by MTT assay (Data are shown as the mean ± SD of 6 replicate groups. Significance levels are expressed by asterisks: $^{**}P < 0.01$ and $^{***}P < 0.001$.) (Reprinted with permission from Ref. [178]; Copyright (2014) Wiley-VCH)

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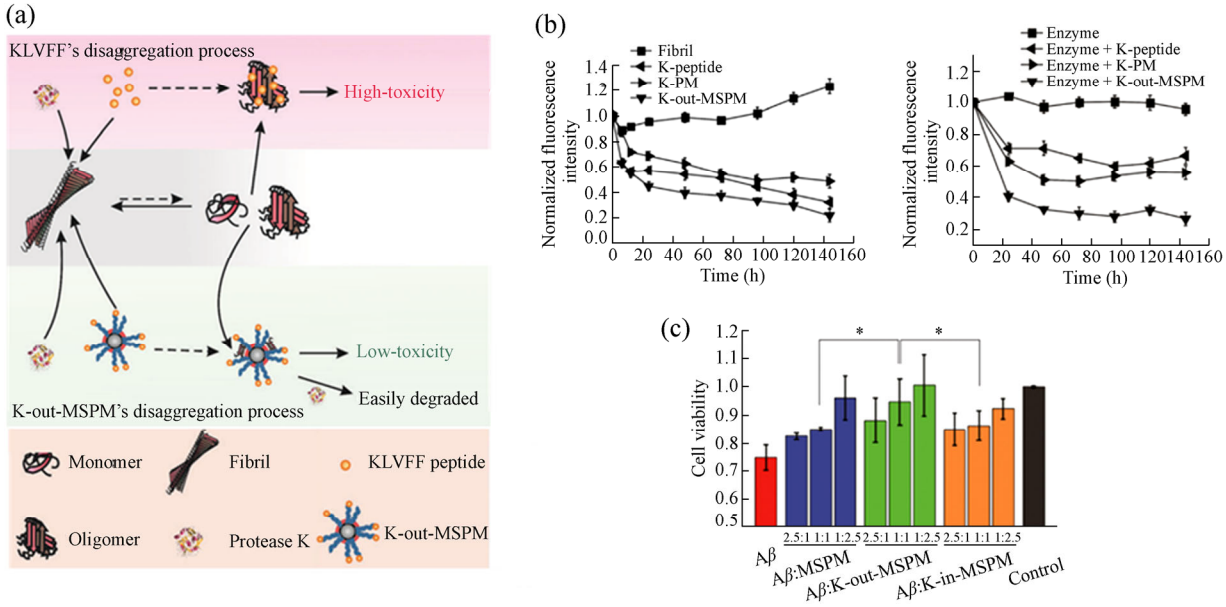

Fig. 13 The synergistic effect between KLVFF and self-assembly chaperones on both disaggregation of beta-amyloid fibrils and reducing consequent toxicity: (a) Schematic of degradation process of K-out-MSPM and KLVFF peptide and the mechanism of reducing potential toxicity by K-out-MSPM; (b) Disaggregation of fibrils by K-peptides, K-PMs, and K-out-MSPMs with or without proteases measured using the ThT fluorescence assay; (c) Reduction of Aβ toxicity by different concentrations of three MSPMs separately (Cell viability was measured using the MTT assay. Significance levels are expressed as asterisks: $^{*}P < 0.05$.) (Reprinted with permission from Ref. [185]; Copyright (2017) The Royal Society of Chemistry)

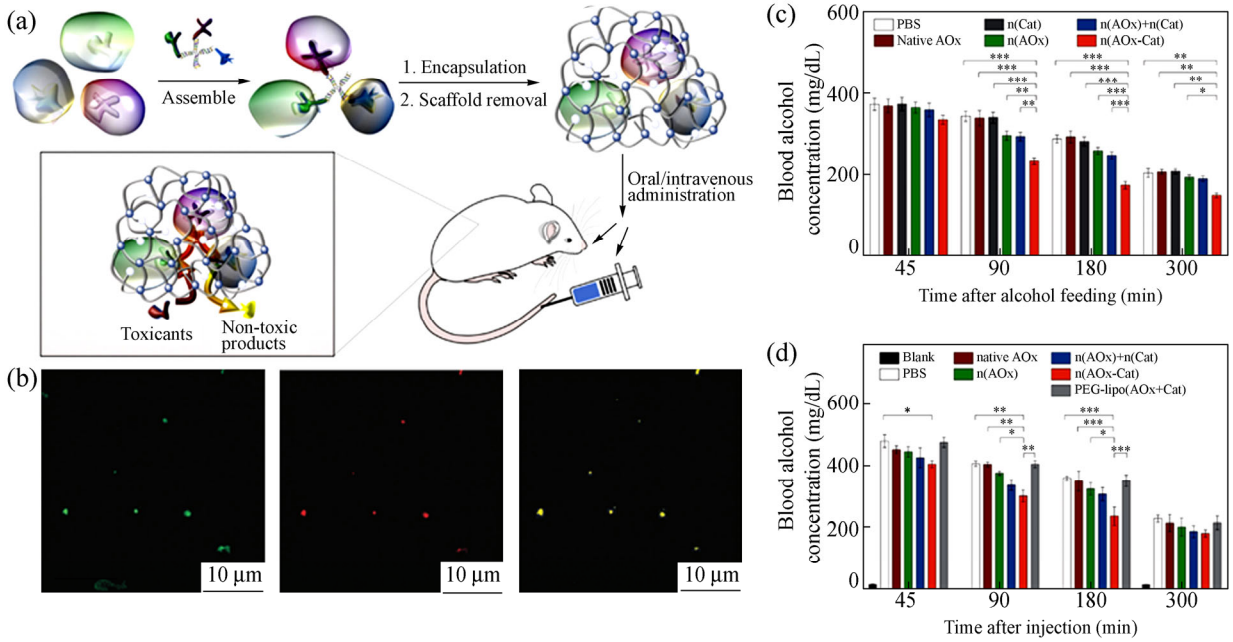

Fig. 14 Enzyme therapeutics for systemic detoxification: (a) Schematic illustration of the synthesis of a triple-enzyme nanocomplex by DNA-directed assembly and nano-encapsulation (The resulting triple-enzyme nanocomplexes can convert toxicants to non-toxic products in the blood stream through multi-enzyme cascade reactions.); (b) Confocal microscope images of *n*(FITC-labelled GOx) (left, excitation = 488 nm, emission = 510–530 nm), *n*(RhB-labelled HRP) (middle, excitation = 532 nm, emission = 570–600 nm) and *n*(RhB-labelled HRP-FITC labelled GOx) (right, excitation = 488 nm; emission = 570–600 nm); (c) BAC in mice after gavage with an alcohol diet containing PBS, native AOx, n(Cat), n(AOx), a mixture of n(AOx) and n(Cat), or n(AOx-Cat), with equivalent amounts of enzymes (The amounts of AOx and Cat were fixed at 65 and 21 μg, respectively, and the alcohol dosage was fixed at 6 mg ethanol per gram bodyweight); (d) BAC of intoxicated mice after injection with PBS, native AOx, PEG-lipo(AOx + Cat) or n(AOx-Cat) (Thirty minutes before injection, mice were gavaged with the alcohol diet at 6 mg ethanol per gram bodyweight. The volumes of PBS and enzyme solutions injected were maintained at 150 mL. The dose of enzyme injected was maintained at 65 μg AOx or 21 μg Cat per mouse.) (Reprinted with permission from Ref. [193]; Copyright (2012) Nature Publishing Group)

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Infectious Diseases

Infections by pathogenic microorganisms are always the huge threats to global health. In recent years, extensive antimicrobial drugs (*e.g.*, β-lactams, ampicillin, penicillin, clindamycin, and tetracyclines, *etc*.) have been approved to kill or inhibit the growth of microorganisms, and to reduce morbidity and mortality[194, 195]. However, a large part of antimicrobial drugs are severely limited when used in clinical settings owing to their low solubility, poor membrane permeability, nonspecific cytotoxicity, and rapid degradation or clearance out of blood stream, which subsequently cause inadequate therapeutic index and local or systemic side effects (*e.g.*, cutaneous irritation, peeling and gut flora reduction, *etc*.)[196, 197].

In addition to above-mentioned limitations, biofilms, a kind of mature extracellular polymeric substances called the glycocalyx produced by microorganisms communities, can also cause persistent bacterial infections and are extremely recalcitrant to antimicrobials, resulting in the reduction of the penetration of antimicrobials which makes bacteria survive in antimicrobial treatment[198]. More importantly, biofouling consisting of microorganisms and biofilms confers many disadvantages and undesirable effects to the surfaces in medical devices, such as occlusion of cardiovascular implants and contact lenses, *etc*.

With the development of nanotechnology, various nanoparticles including liposomes and self-assembled polymeric nanoparticles are developed as innovative and promising systems to overcome these problems and assist the antimicrobials deliver to microbial infection sites[6, 199–202]. Especially for liposome based systems, several of them have been approved for clinical uses, because the antimicrobials embedded in it can be expediently released to the cell membranes or inside the bacteria. AmBisome schlepping amphotericin B is an FDA approved liposome, which has been extensively used to treat fungi infections including *Aspergillus spp*., *Candida spp*. and *Fusarium spp*.[203, 204]. Compared with free benzyl penicillin, liposomal benzyl penicillin has effectively inhibited the growth of penicillin-sensitive strain of *Staphylococcus aureus*[205]. Liposomal teicoplanin and vancomycin have shown significant growth-inhibition and intracellular killing of methicillin-resistant *Staphylococcus aureus*[206, 207]. It has also been reported that the ampicillin-loaded liposomes showed prominent antimicrobial efficacy than free drugs when applied to *Salmonella typhimurium*[208].

Self-assembled polymeric nanoparticles based on biocompatible and biodegradable amphipathic polymers have also been widely used for controlled drugs release in the field of antibiosis and various infectious diseases[209, 210]. For example, the saquinavir loaded poly(ethylene glycol)-block-poly(ε-caprolactone) (PEG-*b*-PCL) nanoparticles can serve as a targeted drug delivery system for eradicating the viral sanctuaries in patients infected with HIV-1/AIDS due to an effective delivery to macrophages[211]. Halofantrine-loaded poly(ethylene glycol)-block-poly(lactide) (PEG-*b*-PLA) nanoparticles could achieve a more favorable halofantrine profile in the plasma, leading to the reduction in intravenous dose and side-effect compared to the free drugs, thus suggesting the use of halofantrine by a parenteral route in severe malaria[212].

Recently, Liu *et al.* prepared a surface-adaptive, triclosan-loaded mixed-shell polymeric-micelles (MSPM), which possessed a shell consisting of hydrophilic poly(ethylene glycol) (PEG) and pH-responsive poly(β-amino ester) that is positively charged at pH = 5.0, while converts to negatively charged at physiological pH conditions (Fig. 15)[213]. The novel structure showed enhanced biofilm penetration and accumulation as a result of the negatively charged bacterial cell walls and the positively charged MSPMs in the acidic biofilm. This approach provided an effective method to by-pass biofilm recalcitrance and assist the penetration of antimicrobials. Li *et al.* reported an enzyme-responsive reside with bacterial strain-selectivity for combating against virulent resistant pathogens (Fig. 16)[214]. The penicillin G amidase (PGA) and β-lactamase (Bla) responsive vesicles were self-assembled from amphiphilic diblock copolymers consisting of a PEG segment and the hydrophobic segment containing enzyme-cleavable side linkages. In response to the enzymes, which were closely associated with drug-resistant bacterial strains, the antimicrobial-loaded vesicles underwent a process of self-immolative structural rearrangement and morphological transitions by side-chain degradation on hydrophobic segment, leading to the sustained release of drugs.

Besides the antimicrobials containing delivery systems, several polymers also displayed remarkably antimicrobial activity by themselves[194, 215], since the bacterial cell walls are negatively charged while antimicrobial polymers are usually positively charged, such as polymers with amine or guanidine. It is generally accepted that the mechanism of bactericidal action is the destructive interaction between polycationic biocides and the cell wall or cytoplasmic membranes. However, clinical applications of these polymers are compromised by poor bioavailability and limited diffusion in tissues. Insua *et al.* presented a novel enzyme-responsive polyion complex (PIC) nanoparticle self-assembled from cationic poly(ethylene imine) (PEI) and an anionic *P. aeruginosa*'s elastase (LasB)-responsive peptide. Such nanoparticles could selectively deliver the antimicrobial polymers to *Pseudomonas aeruginosa*, whose infections were extremely tricky to treat (Fig. 17)[216].

CONCLUSIONS AND PERSPECTIVES

Aiming at the possible pathogenesis of different diseases, various drugs have been developed during the past decades. However, the instability and serious side effects of the drugs weaken their efficiency. Rapid development of self-assembled systems as drug carriers has promised a significant improvement to eliminate these obstacles (several have been approved for clinical treatments), benefiting from notable advantages of self-assembly. For instance, the formation of drug carriers by self-assembly is flexible to control the sizes, shapes and surface properties, exhibiting lower toxicity, prolonged half-life and better targeting capability. According to the biological characteristics of

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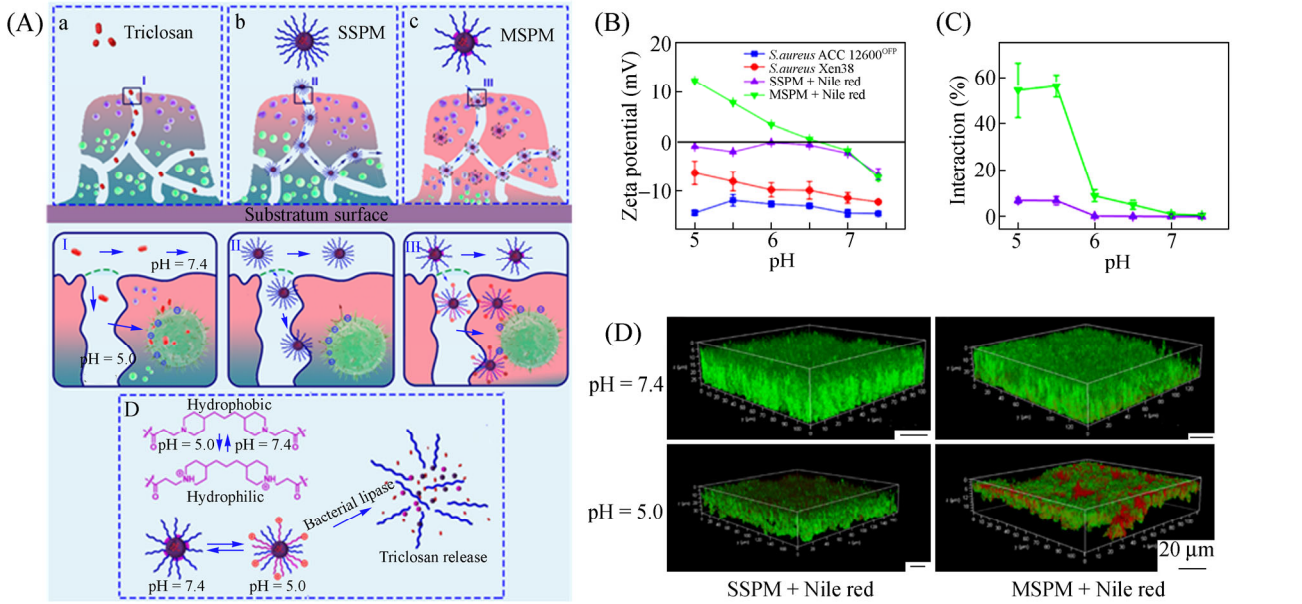

Fig. 15 Surface-adaptive, antimicrobially loaded, micellar nanocarriers with enhanced penetration and killing efficiency in staphylococcal biofilms: (A) (a) Nonencapsulated antimicrobials penetrating to a limited degree into a biofilm and killing only bacteria on the outside of the biofilm (Penetration is limited by adsorption to bacterial cell surfaces and matrix components.), (b) antimicrobials encapsulated in a single-shell polymeric micelles (SSPMs) with stealth properties showing better penetration into a biofilm than nonencapsulated ones (However, due to the stealth properties of the SSPMs, there will be no targeting to bacterial cell surfaces and, as a consequence, little enzymatic degradation of micelles and antimicrobial release.), (c) antimicrobials encapsulated in a mixed-shell polymeric micelles (MSPMs) with stealth properties showing full penetration in a biofilm due to their stealth properties and becoming positively charged in the low pH vicinity of bacteria to target themselves to the bacterial cell surface and expose their micelle core (The micelle core subsequently becomes hydrolyzed by bacterial lipases to release its antimicrobial content.), and (d) summary of the surface-adaptability of MSPMs under the influence of pH changes and lipase degradation; (B) Zeta potentials of Nile red loaded SSPM and MSPM micelles in 10 mmol/L phosphate buffer as a function of pH; (C) Interaction between Nile red loaded micelles and planktonic *S. aureus* ATCC12600^{GFP} as a function of pH; (D) Penetration and pH-dependent bacterial targeting of Nile red loaded micelles in a staphylococcal biofilm (Reprinted with permission from Ref. [213]; Copyright (2016) American Chemical Society)

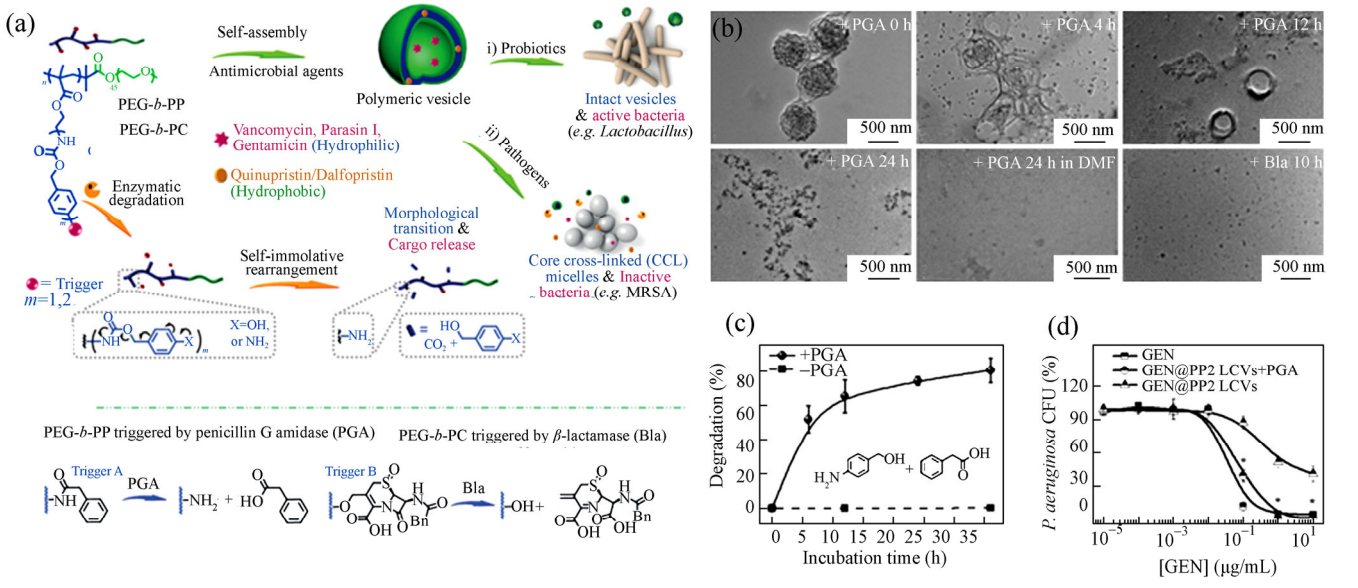

Fig. 16 Enzyme-responsive polymeric vesicles for bacterial-strain-selective delivery of antimicrobial agents: (a) Enzyme-responsive polymeric vesicles for bacterial-strain-selective delivery of antibiotics (Polymeric vesicles self-assembled from PEG-*b*-PP and PEG-*b*-PC are subjected to side chain cleavage and microstructural transformation in response to PGA, and Bla, respectively. This process is accompanied with sustained release and bioactivity recovery of antimicrobial agents encapsulated within vesicles.); (b) Time-dependent evolution of PGA-digested PP2 large compound vesicles (LCVs); (c) Percentage degradation of PP2 LCVs against incubation duration in the absence and presence of PGA; (d) Gentamicin (GEN)-equivalent concentration dependent *P. aeruginosa* inhibition of GEN, GEN-loaded PP2 LCVs in the absence and presence of PGA (Reprinted with permission from Ref. [214]; Copyright (2016) Wiley-VCH)

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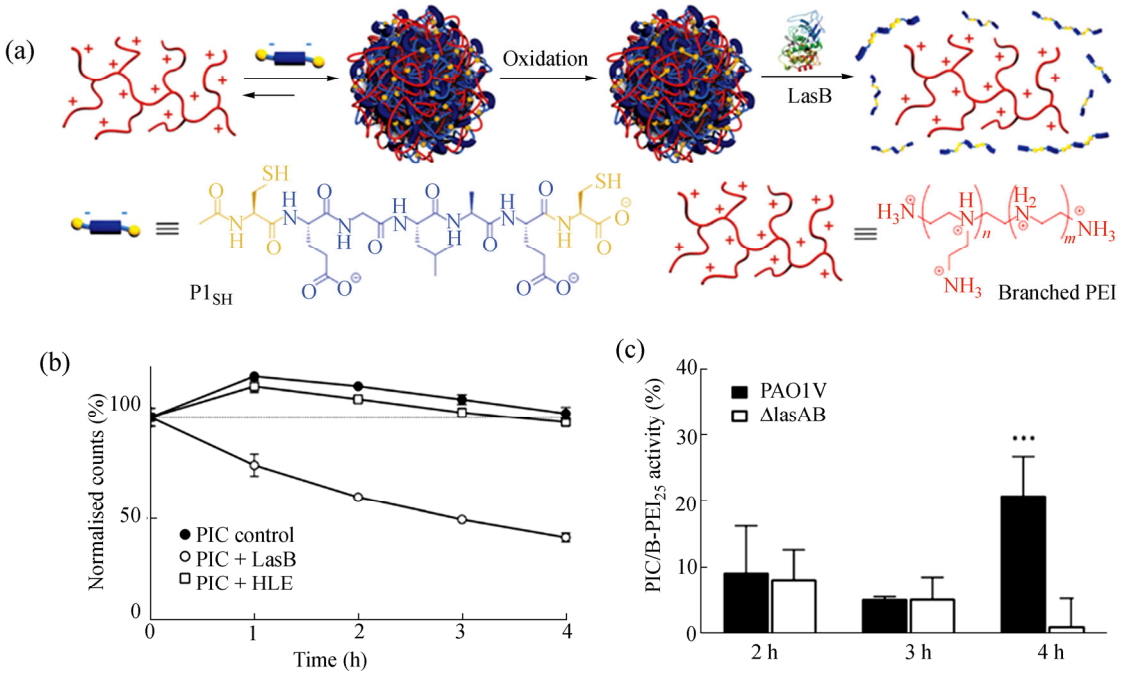

Fig. 17 Enzyme-responsive polyion complex nanoparticles for the targeted delivery of antimicrobial polymers: (a) Assembly and oxidative cross-linking of PIC nanoparticles from $P1_{SH}$ (Ac-C-E-GLA-E-C-OH) and antimicrobial branched PEI, degradation of PIC nanoparticles by LasB and subsequent PEI release; (b) Normalised detection counts (%) for $P1_{SH}$ PIC nanoparticles in the absence (●) and presence of LasB (○) and HLE (□) (Data are normalised to the initial counts for each of the individual experiments. n = 3.); (c) Normalised antimicrobial activity over time of $P1_{SH}$ PIC nanoparticles (*** $P < 0.001$ between PAO1V (secrete LasB) and ΔlasAB (not secrete LasB) (CI = 99.9%) after 4 h. n = 3.) (Reprinted with permission from Ref. [216]; Copyright (2016) The Royal Society of Chemistry)

different diseases (*e.g.*, pH, enzymes, temperature, adenosine triphosphate (ATP), and glucose, *etc.*), a variety of stimuli-responsive self-assembled systems have been designed for the controlled release of drugs. In addition, self-assembly has also been used as an effective strategy to construct targeted drug delivery systems as well as combinatory therapy with high precision and selectivity.

Despite great efforts made to the applications of self-assembled nano-therapeutics, several challenges remain to be overcame. Firstly, new materials, especially PEG-alternatives as well as new types of responsive polymers, are highly demanded for nano-carriers to overcome biological barriers *in vivo*. Secondly, targeting capability of self-assembled nano-carriers needs to be further enhanced for the precise delivery of drugs to their desired targets in order to achieve optimal therapeutic effects and minimize potential side-effects. Finally, integration of modern therapeutic methods, especially immunotherapies, should be taken into consideration in the design of new generation of nano-medicines for disease treatments.

In conclusion, introducing self-assembly into nanotechnology has brought great convenience to the development of advanced drugs for disease treatments. Nowadays, nano-therapeutics have been developed to an impressive stage with the ability to perform site-specific delivery with temporal and spatial control. Given recent advances in nanotechnology along with knowledge accumulated, we believe that self-assembled nano-systems will become one of the essential technologies for the development of new drugs in the near future.

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