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Polypeptide-based drug delivery systems for programmed release

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ABSTRACT

Recent years have seen increasing interests in the use of ring-opening polymerization of α-amino acid *N*-carboxyanhydrides (NCAs) to prepare synthetic polypeptides, a class of biocompatible and versatile materials, for various biomedical applications. Because of their rich side-chain functionalities, diverse hydrophilicity/hydrophobicity profiles, and the capability of forming stable secondary structures, polypeptides can assemble into a variety of well-organized nano-structures that have unique advantages in drug delivery and controlled release. Herein, we review the design and use of polypeptide-based drug delivery system derived from NCA chemistry, and discuss the future perspectives of this exciting and important biomaterial area that may potentially change the landscape of next-generation therapeutics and diagnosis. Given the high significance of precise control over release for polypeptide-based systems, we specifically focus on the versatile designs of drug delivery systems capable of programmed release, through the changes in the chemical and physical properties controlled by the built-in molecular structures of polypeptides.

1. Introduction

Polypeptide-based materials are promising candidates for biomedical applications, mainly due to the excellent biocompatibility, the satisfactory biodegradability, and the versatile side-chain designs of polypeptides [1–5]. In addition, polypeptide materials adopt stable secondary structures including α-helices and β-sheets. Compared with unstructured polymers, polypeptides with ordered secondary structures exhibit unique self-assembly behaviors and interesting biological properties [6,7]. Synthetic polypeptide materials are usually prepared through recombinant technology, solid-phase peptide synthesis (SPPS), and ring-opening polymerization (ROP) of α-amino acid *N*-carboxyanhydrides (NCAs). Among these three strategies, ROP of NCAs provides a straightforward route to high-molecular-weight synthetic polypeptides in large scale, enabling the design of a library of biomaterials with rich chemical and physical diversity [8]. With the development of a variety of well-controlled ROP chemistry [9,10], polypeptides can be easily integrated with other non-peptidic materials, endowing hybrid materials with even more versatile features for self-assembly and controlled release. The polypeptides and polypeptide-based hybrid materials are particularly pursued for their use in drug delivery because of their biocompatibility, biodegradability, and tunable secondary structures [1,2,4,5,11]. Polypeptides with inherent therapeutic activity, such as Copaxone (glatiramer acetate) and VivaGel, have reached clinical success for the treatment of cancer and autoimmune disease [12–15]. Some of the polypeptide-based systems have been evaluated through various stages of clinical trials [16,17].

To enhance the temporal and spatial availability of therapeutic agents in a defined target, it is desirable to have an effective drug delivery system (DDS) that is stable against the dilution in biological media, possesses stealth properties to avoid uptake by the reticuloendothelial system, targets the disease tissues, and releases drugs in the

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disease tissues in a controlled manner [18]. Whiles polymeric micelles or polymeric nanoparticles based on FDA-approved polyesters (*e.g.*, poly (lactic acid) (PLA) and poly(lactic-*co*-glycolic acid) (PLGA)) are widely used, one of their key drawbacks is the lack of side-chain functionality, which provides limited approaches to stabilize the delivery vehicles other than hydrophobic interactions. Poorly controlled self-assemblies with multimodal particle distribution and instability of the nano-structures are often observed [19]. As a result, undesired release of drugs is often inevitable from the self-assembled nano-delivery systems based on polyesters, mainly due to the intrinsic properties such as amorphous structures and bulk erosion profiles [20,21].

Polypeptide materials adopt ordered secondary structures (*e.g.*, α-helices and β-sheets) and have much more versatile side-chain functionalities than polyesters [22], which enable the fine tuning of materials properties for better stability profiles. Versatile nano-structures other than micelles and nanoparticles, such as vesicles, are easily obtainable with polypeptides bearing α-helical segments [23], which provides additional control over drug release and enables the facile formulation of hydrophilic drugs (*e.g.*, proteins and nucleic acids). Besides the unique advantage of the helix-induced assembly behaviors, the rich side-chain functionalities of polypeptides not only provide sites for the covalent conjugation of drugs and facile crosslinking for enhanced structural stability, but also enable the manipulation of the physical properties of the resulting nano-assemblies through the design of smart, trigger-responsive chemistry. The design of smart chemistry for programmed release in DDSs is an important strategy to minimize undesired toxicity and maximize the efficacy [24–26]. Various functionalities responsive to the internal or external stimuli were incorporated onto the polymers, which trigger the on-demand release of payloads at target site. Controlled release is therefore possible through tuning of the built-in molecular structures of the polypeptide segments, which is otherwise difficult to reach in the delivery systems based on other biopolymers.

In this review, we summarize the trigger-responsive designs for programmed release of payloads in polypeptide-based DDSs over the last two decades. Specifically, the materials designs, strategies, and mechanisms for the loading and triggered release of cargos in the multi-functional, polypeptide-based carriers are highlighted and discussed (Fig. 1), which shed light on the future design of smart polypeptide-based drug carriers. This review focuses on polypeptide materials derived from NCA polymerization. Therefore, smart peptide or polypeptide materials from other preparation methods are beyond the scope of the current review. We believe this review serves as a nice complement to the existing review articles on polypeptide materials focusing on the materials design [3–5,10,11,27–31], self-assembly [32,33], secondary structure [6,7], and biomedical applications [1–5,11,15,33–46].

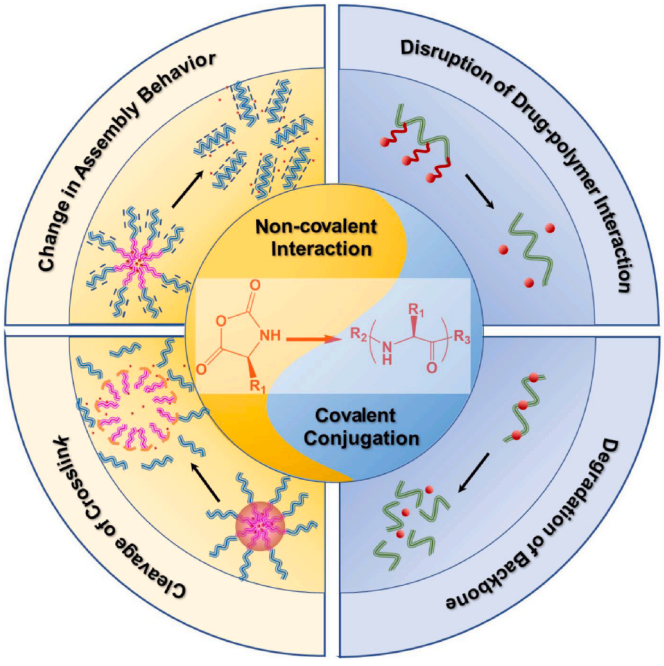


Fig. 1. The schematic illustration of trigger-responsive release of payloads in polypeptide-based drug-delivery systems.

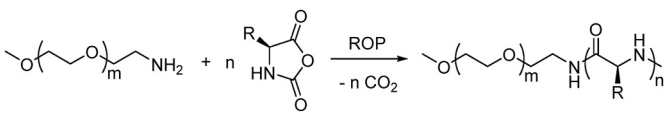
2. Release of payloads through the changes in polypeptide assembly behaviors

The most common strategy to load hydrophobic drugs is the assembly of amphiphilic block copolymers in aqueous environment, followed by the physical encapsulation of payloads through hydrophobic interactions and/or other interactions. Specifically for polypeptide-based carriers, amphiphilic poly(ethylene glycol)-*block*-polypeptide (PEG-*b*-polypeptide) are widely studied as drug delivery vehicles due to the ease of preparation. The ROP of NCA monomers with methoxy poly (ethylene glycol) amine (mPEG-NH_2) as the macroinitiator results in well-defined diblock copolymers in one step (Scheme 1). A representative PEG-*b*-polypeptide-based agent, NK-105, has been advanced into Phase III clinical studies by Nippon Kayaku Co [47–49]. NK-105 is assembled from 4-phenyl-1-butanol-modified PEG-*b*-poly(aspartic acid) (PAsp), which is further loaded with paclitaxel (PTX) by physical entrapment, exhibiting acceptable activity and good tolerability. In addition, various polypeptides served as the hydrophobic segments in the design of PEG-*b*-polypeptide drug carriers, such as poly(γ-benzyl-$_L$-glutamate) (PBLG) [50], poly(β-benzyl-$_L$-aspartate) (PBLA) [51], poly(ε-carbobenzyloxy-$_L$-lysine) (PZLL) [52], poly($_L$-phenylalanine) (PPhe) [53], and poly($_L$-leucine) (PLeu) [54] (Scheme 2). Nevertheless, the release of payloads from these vehicles rely on the dilution under physiological conditions and the enzymatic degradation of polypeptide segments [55], which are difficult to control. Therefore, the incorporation of smart chemistry enables the *in situ* change in the assembly behavior of polypeptide segments, facilitating the controlled release of payloads at target sites.

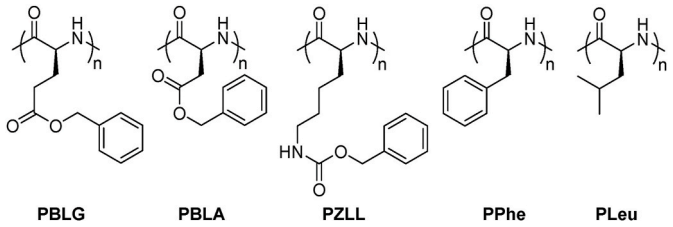
Stimuli-responsive hydrophobic-to-hydrophilic transition is a well-known strategy to destabilize the nano-assemblies from amphiphilic block copolymers [56,57]. In the case of PEG-*b*-polypeptide vehicles, for example, the transition renders the polypeptide segments partially or completely water-soluble, facilitating the disassembly of nano-carriers and the release of encapsulated hydrophobic drugs. Besides the materials design to promote the hydrophobic-to-hydrophilic transition, a strategy that is widely used in various polymer-based drug carriers, the assembly behavior of polypeptide-based materials is also controlled by their secondary structures [7], which offers additional method to tune the release of cargos. Based on the specific type of triggers, we discuss the polypeptide-based DDSs with stimuli-responsive changes in copolymer assembly behaviors, and highlight the materials design and disassembly mechanism of the drug carriers.

2.1. pH-responsive changes in assembly behaviors

The pH-responsive design is one of the most common strategy to selectively release cargos at the targeted tumor sites, mainly due to the acidic extracellular environment in tumor tissues [58]. Several polypeptide segments with pH-responsive protonation behaviors were incorporated as the hydrophobic segments, including poly($_L$-glutamic



Scheme 1. Synthetic route to PEG-*b*-polypeptide diblock copolymers from ROP of NCAs using mPEG-NH_2 as the macroinitiator.



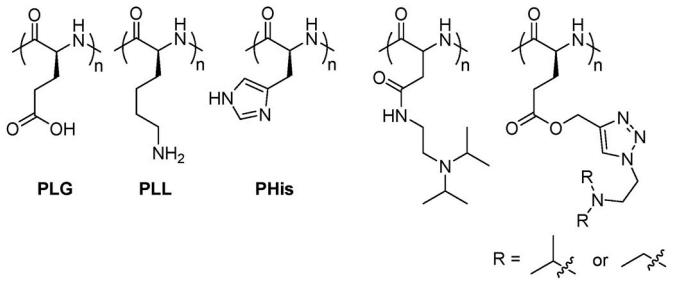
Scheme 2. Chemical structures of representative hydrophobic segments in the design of PEG-*b*-polypeptide drug carriers.

acid) (PLG) [59], poly(L-lysine) (PLL) [60], poly(L-histidine) (PHis) [61–64], and tertiary-amine functionalized polypeptides [65,66] (Scheme 3). These polypeptide blocks became hydrophilic at the charged state, triggering the disassembly of the nano-carriers. In order to enhance the stability of the nano-assemblies, hydrophobic polypeptide residues were incorporated through copolymerization or blending of copolymers. For example, PEG-*b*-PHis showed stability issues at pH 7.4 [67], limiting their application as drug delivery carriers. Through the copolymerization with L-phenylalanine NCA, the pKa value of the PEG-*b*-(PHis-*co*-PPhe) was manipulated by the fraction of His and Phe residues, with lower pKa observed at higher Phe/His ratio [68]. Additionally, the stability of micelles was also improved by blending PEG-*b*-PHis with PEG-*b*-PLA, with the ratios between the two polymers exhibited great impact on the micellar stability [61]. The carriers consisting of 25 wt% PEG-*b*-PLA showed satisfactory stability at pH 7.4, while still rapidly release encapsulated doxorubicin (DOX) at lowered pH.

Besides micelles, the amphiphilic copolymers with hydrophobic, α-helical polypeptide segments also formed stable vesicles, mainly due to the side-by-side packing of rigid, rode-like α-helices. Polypeptide vesicles bearing pH-responsive residues are therefore promising candidates as drug carriers with their ability to load hydrophilic cargos [23,69]. Deming and co-workers prepared amphiphilic copolypeptides with hydrophobic, α-helical PLeu-*co*-PLL blocks, which formed vesicles under basic conditions. Upon acidification of the solution, the protonation of PLL residues led to disruption of both helicity and the hydrophobicity (Fig. 2), resulting in the disassembly of vesicles and the release of the encapsulated Fura-2 dye, which serves as an example of the release of hydrophilic molecules in a controlled manner and provides a reference to design pH-sensitive drug delivery systems [23].

2.2. Redox-responsive changes in assembly behaviors

The redox-responsive chemistry has been intensively exploited in DDSs, as the differences in redox potentials were found in tissues and cellular compartments [70–73]. Specifically, while the low level of reactive oxygen species (ROS) was observed in normal tissues, the overexpression of ROS in diseased tissues results in oxidative stress that damages the cells. Methionine, a natural amino acid bearing thioether side chains, is one of the most important antioxidant residues to defend



Scheme 3. Chemical structures of representative polypeptide segments with pH-responsive (de)protonation behaviors.

the body against ROS [74]. Deming and co-workers reported the preparation of poly(L-methionine) (PMet)-based copolypeptides, PMet-*b*-(-PLeu-*co*-PPhe), which became amphiphilic after the oxidation of PMet block into poly(L-methionine sulfoxide) (Scheme 4) [75]. The resulting copolypeptide vesicles exhibited enzyme-triggered disassembly and the release of model hydrophilic cargo, Texas Red-labeled dextran. Different from the strategy of most other DDSs that the disassembly is mediated by the hydrophobic-to-hydrophilic transitions, this work represents an example of disassembly triggered by the hydrophilic-to-hydrophobic transition. The rupture of vesicle membrane was attributed to the transformation of disordered, hydrophilic poly(L-methionine sulfoxide) into α-helical, hydrophobic PMet, leading to the aggregation of copolypeptides (Fig. 3A). Additionally, PMet was directly used as the hydrophobic blocks to form micelles and hydrogels [76,77]. For instance, Chen, He, and co-workers developed ROS-responsive PEG-*b*-PMet hydrogels, which showed accelerated erosion in the presence of H_2O_2 and the release of encapsulated cargos [76].

Other than PMet, side-chain thioethers were also introduced into polypeptides using cysteine as the building blocks through thiol-based chemistry, including thiol-ene click chemistry, Michael addition, or nucleophilic substitution (Scheme 4) [78–80]. In addition, selenoether were also added onto the polypeptide side chains (Scheme 4) [81]. These polypeptides exhibited oxidation-responsive change in secondary structures, which offers promising chemistry for the design of drug delivery vehicles. For instance, Ding and co-workers reported the preparation of PEG-*b*-poly(cysteine) (PCys) derivative bearing side-chain thioethers with terminal cholesterol groups (Scheme 4 and Fig. 3B) [82]. The H_2O_2 treatment resulted in the thioether-to-sulfone transition and the conformational change from β-sheets to α-helices, which induced a micelle-to-vesicle transformation as revealed by cryo-TEM images (Fig. 3C and D). The nanocarrier was further used to load DOX, which exhibited oxidation-responsive release of payloads due to the transformation of the morphology.

Gu, Shen, and co-workers developed an anaerobe-inspired, polypeptide-based nanovesicle, which was activated in tumor hypoxic regions to destroy cancer cells [83]. Two PEG-*b*-poly(serine) (PSer) derivatives were synthesized to form the nanovesicles, which was used to encapsulate the hypoxia-activatable drug, tirapazamine (TPZ) (Fig. 4A). The photosensitizer-conjugated PEG-*b*-PSer derivative (PEG-Poly(Ser-Ce6)) was able to consume intracellular oxygen and generate ROS at the tumor region upon light irradiation, creating a local hypoxic environment. The generated ROS oxidized the thioether groups into sulfone groups on the other copolymers (PEG-Poly(Ser-S-NI)), whose side-chain 2-nitroimidazoles were bioreduced into 2-aminoimidazoles under hypoxic conditions. (Fig. 4B). Both structural changes resulted in the hydrophobic-to-hydrophilic transition of the polypeptide segments of PEG-Poly(Ser-S-NI), disrupting the nanovesicles and triggered the release and activation of loaded TPZ for tumor inhibition (Fig. 4C and D).

2.3. Glucose-responsive changes in assembly behaviors

Glucose-responsive insulin delivery system is one of the most promising strategy to treat diabetes, with three well-established approaches involving glucose oxidase (GOx), glucose binding proteins, and phenylboronic acid (PBA) [84–86]. Among these three approaches, PBA-functionalized polymers offer a completely synthetic way to prepare the delivery carrier [87]. PBA is capable of reversibly binding with glucose by forming a five- or six-member cyclic boronic ester, accompanied by an increase in hydrophilicity. Taking advantage of this transition, Chen group reported a glucose-responsive insulin delivery system from PBA-modified PEG-*b*-PLG (Scheme 5A) [88]. The resulting micelles protected encapsulated insulin from undesired enzymatic degradations, and released the insulin in a glucose-dependent manner. An obvious increase in cumulative insulin release was observed at higher glucose concentration, with 12.6% and 32.8% insulin release after 3 h at a

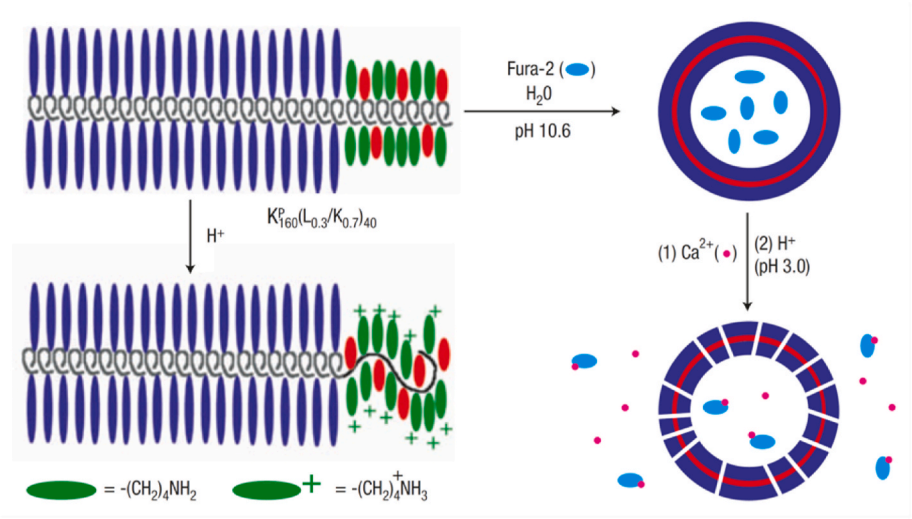
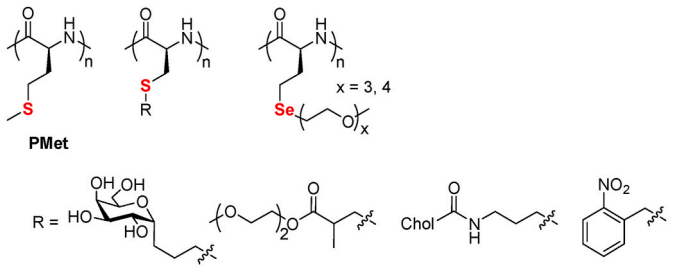


Fig. 2. Schematic illustration of pH-responsive polypeptide vesicle with acid-induced release of entrapped Fura-2 dyes. The disassembly was attributed to the change in both hydrophobicity and secondary structure. Reprinted with permission from Ref. [23]. Copyright 2004 Springer Nature.



Scheme 4. Chemical structures of redox-responsive polypeptides bearing thioether or selenoether side chains.

glucose concentration of 0 and 5.0 mg mL^{-1}, respectively (Fig. 5A and B). In a similar approach, Shi and co-workers developed glucose-responsive micelles using copolymers bearing PBA-functionalized PAsp segments (Scheme 5A) [89]. Through the changes in glucose concentration, repeated on-off release of insulin was achieved.

In addition to the PBA approach, Gu group combined the GOx strategy with H_2O_2-responsive, polypeptide-based vesicles for the self-regulated delivery of insulin [90]. GOx is a common glucose sensor, which catalyzes the oxidation of glucose by oxygen, generating gluconic acid and H_2O_2 (Scheme 5B). The authors prepared polypeptide-based vesicles with phenylboronic ester (PBE)-modified PSer as the hydrophobic segments (Scheme 5C), into which GOx and insulin were loaded in the aqueous cavity. Under high glucose concentration, the glucose molecule diffused across the vesicle membrane and was oxidized inside the aqueous cavity. The generation of H_2O_2 from glucose oxidation triggered the degradation of PBE side chains and the subsequent disassembly of vesicles (Fig. 5C). In addition, the vesicles were further incorporated with a microneedle-array patch for convenient and painless administration. The release of insulin was sensitive to the glucose concentration, with a pulsatile release pattern observed by periodically switch the glucose concentration between 100 and 400 mg/dL (Fig. 5D and E). Since the GOx-catalyzed oxidation of glucose generates acid and consumes oxygen, the same research group also coupled the GOx strategy with vesicles from PEG-*b*-PSer derivatives with pH-responsive and hypoxia-/H_2O_2-dual responsive properties (Scheme 5C) [91,92].

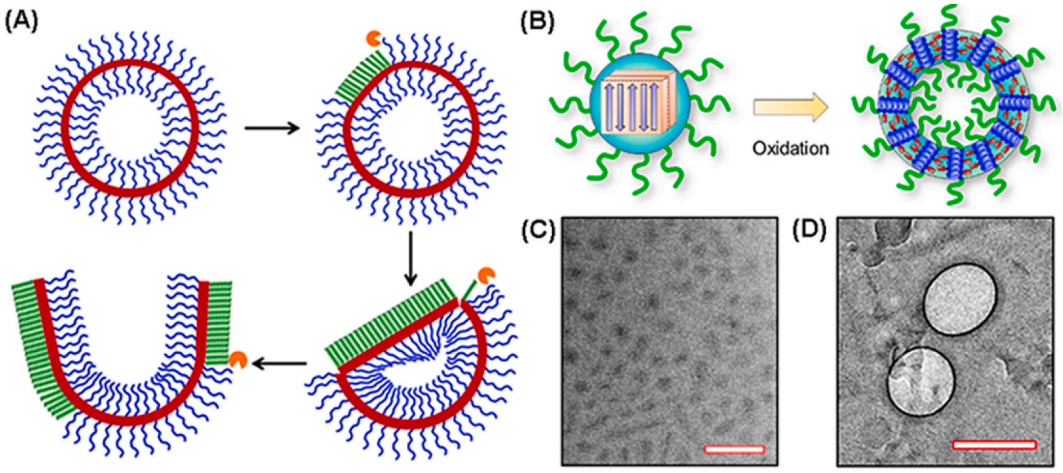


Fig. 3. Representative polypeptide-based DDSs with redox-responsive changes in assembly behavior. (A) Schematic illustration of the enzyme-triggered vesicle based on the reduction of side-chain methionine sulfoxide groups. Reprinted with permission from Ref. [75]. Copyright 2013 American Chemical Society. (B) Schematic representation of the oxidation-responsive micelle-to-vesicle transformation from copolymers based on cholesterol-modified PCys. (C, D) Cryo-TEM images of the assemblies based on cholesterol-modified PCys before (C) and after oxidation (D). Scale bar = 100 nm. Reprinted with permission from Ref. [82]. Copyright 2018 American Chemical Society.

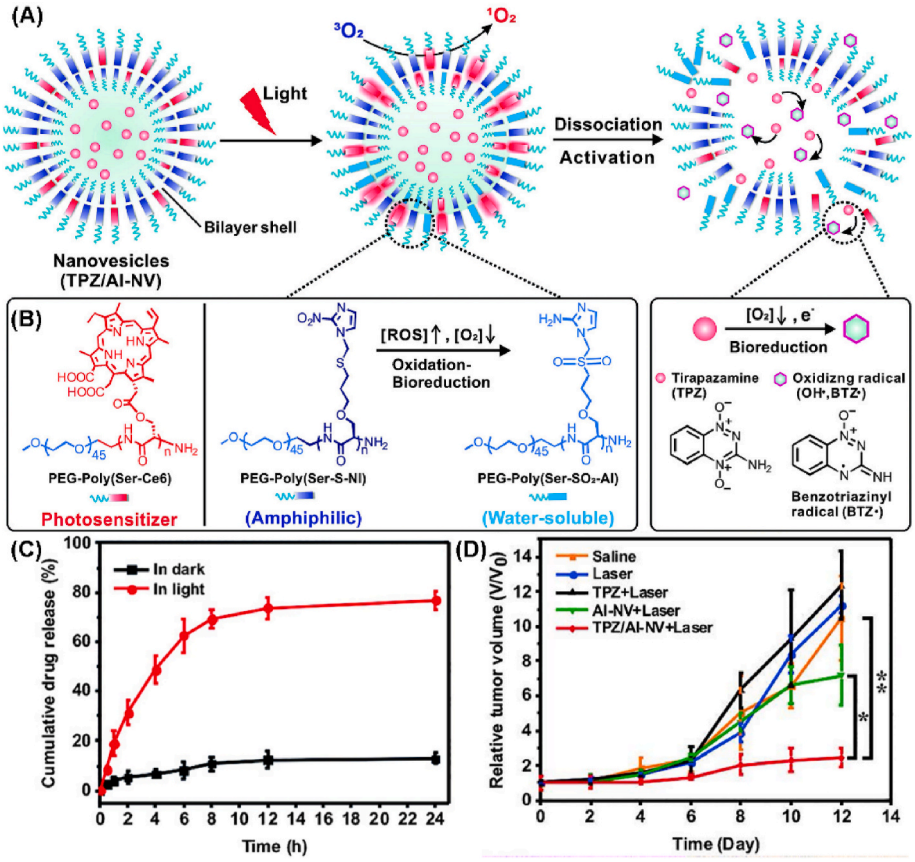
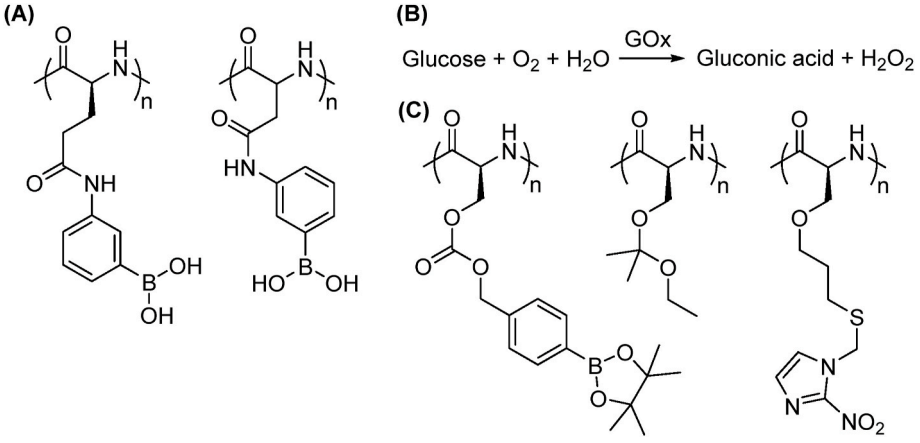


Fig. 4. The anaerobe-inspired, polypeptide-based nanovesicles. (A) Schematic illustration of the assembly and triggered disassembly of nanovesicles. (B) The chemical structures of PEG-Poly(Ser-Ce6), PEG-Poly(Ser-S-NI), and TPZ. PEG-Poly(Ser-S-NI) underwent hydrophobic-to-hydrophilic transition due to ROS- and hypoxia-triggered structural changes. (C) *In vitro* release of TPZ from the nanovesicles in dark or in light. (D) The tumor growth curve after treatment with nanovesicle under laser irradiation (TPZ/AI-NV + Laser). Saline treatment, laser treatment, TPZ without nanovesicle (TPZ + Laser), and nanovesicle without TPZ (AI-NV + Laser) were used as control groups. Reprinted with permission from Ref. [83]. Copyright 2017 John Wiley and Sons.



Scheme 5. (A) Chemical structures of representative polypeptides bearing PBA side chains. (B) GOx-catalyzed oxidation of glucose as glucose sensor. (C) Chemical structures of polypeptide segments used in the design of GOx-mediated glucose-responsive DDSs.

Both systems exhibited smart, glucose-responsive release of encapsulated insulin.

2.4. Light-responsive changes in assembly behaviors

Light-responsive DDSs have been widely studied, as light trigger can be remotely applied with high spatial and temporal precision [93,94]. Several light-responsive groups, including spiropyran [95], coumarin [96], and *o*-nitrobenzyl groups [97–103] (Scheme 6), were attached onto the polypeptide side chains, which mediated the hydrophobic-to-hydrophilic transition and/or the change in secondary structures, resulting in the disassembly of nano-objects. For instance, spiropyran-functionalized PEG-*b*-PLG disassembled upon UV-irradiation, which was attributed to the hydrophobic-to-hydrophilic transition of the polypeptide block because of the spiropyran-to-merocyanine isomerization (Fig. 6A) [95]. In another example, Dong and co-workers reported the formation of micelles from *o*-nitrobenzyl-modified PEG-*b*-PCys, whose polypeptide block adopted a β-sheet conformation [97]. UV light triggered the photo-cleavage of side-chain *o*-nitrobenzyl groups, resulting in a size reduction of the micelles (Fig. 6B). The maintained aggregation status after UV irradiation was attributed to the β-sheet structure of PCys residues with strong intermolecular hydrogen-bonding interactions. Following this work, the same research group incorporated upconversion nanoparticles (UCNPs)

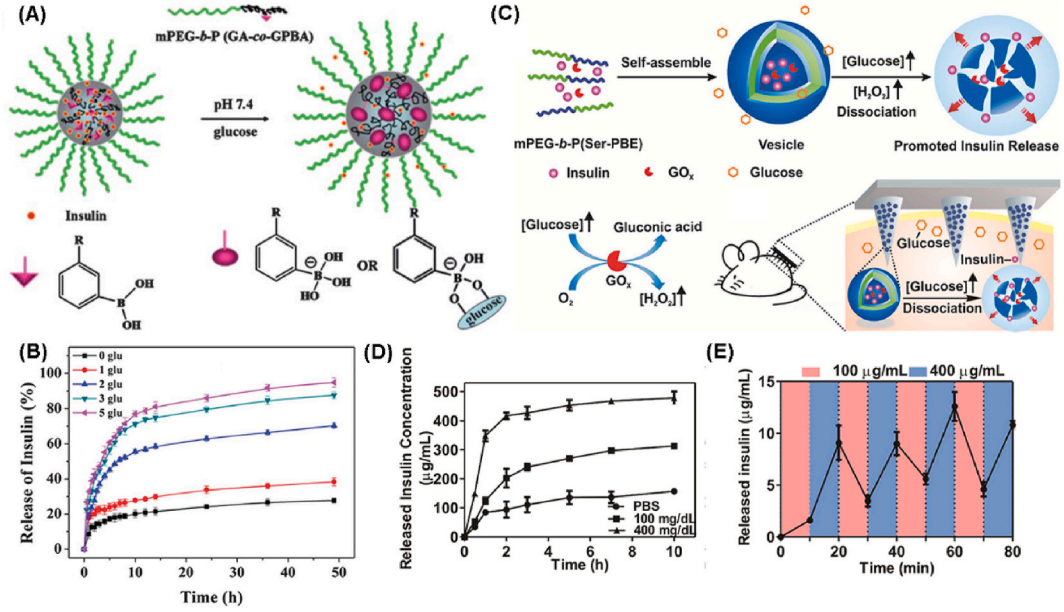
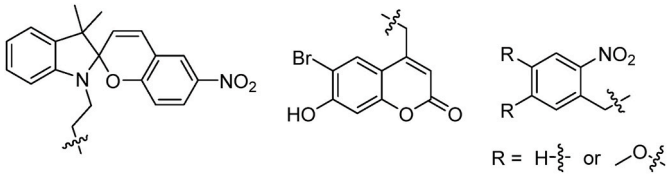


Fig. 5. Representative polypeptide-based DDSs with glucose-responsive changes in assembly behavior. (A) Schematic illustration of glucose-sensitive polypeptide micelle based on PBA strategy. (B) The cumulative release of insulin from PBA-modified polypeptide micelles. Reprinted with permission from Ref. [88]. Copyright 2012 Royal Society of Chemistry. (C) Schematic illustration of glucose-triggered disassembly of GOx and insulin co-loaded polypeptide-based vesicles. (D) *In vitro* release of insulin from GOx and insulin co-loaded vesicles at various glucose concentrations. (E) Manipulation of insulin release through alternating switch of glucose concentration. Reprinted with permission from Ref. [90]. Copyright 2017 American Chemical Society.



Scheme 6. Chemical structures of representative light-responsive groups.

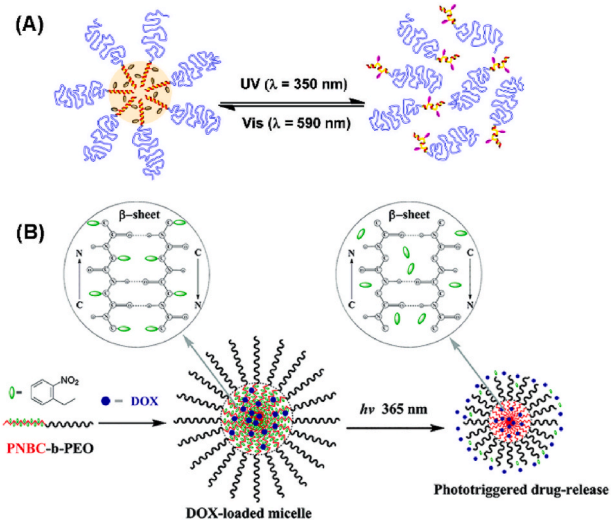


Fig. 6. Representative polypeptide-based DDSs with light-responsive changes in assembly behavior. (A) Scheme illustrating the photo-responsive assembly/disassembly of the spiropyran-functionalized PEG-*b*-PLG due to spiropyran-merocyanine isomerization. Reprinted with permission from Ref. [95]. Copyright 2011 American Chemical Society. (B) UV-responsive disassembly of PEG-*b*-PNBC micelles and release of encapsulated DOX. Reprinted with permission from Ref. [97]. Copyright 2012 American Chemical Society.

into the micelles to achieve near-infrared (NIR) responsiveness [98,99]. NIR light showed deeper tissue penetration and less damage compared with UV light, which is preferable for biomedical applications [93].

Dong and co-workers designed a *S*-nitroso donor conjugated PCys (PNOC), which released nitric oxide (NO) for NO gas therapy [104]. PEG-*b*-PNOC micelles was coated with polydopamine (PDA) and loaded with DOX, resulting in a NIR-responsive nanocomposite for the synergistic triple therapies (*i.e.*, photothermal therapy, NO gas therapy, and chemotherapy) (Fig. 7A). Upon NIR irradiation, the absorbed NIR light by PDA was converted to heat with a high photothermal conversion efficiency, promoting the cleavage of S–NO bond on PNOC. The NIR-dependent release of NO reverse the multidrug resistance (MDR) and enhance the efficiency of photothermal therapy and chemotherapy (Fig. 7B). In addition, the intracellular acidic pH resulted in the protonation of PDA and/or DOX. Coupled with the NIR-promoted DOX diffusion, burst release of DOX was observed (Fig. 7C), elevating the synergistic therapeutic efficacy to eradicate multi-drug resistant tumors with a single injection and a single NIR irradiation.

In addition to the abovementioned light-responsive groups, azobenzene was widely used as light-responsive groups with its *cis-trans* photoisomerization. Several recent papers reported the change in materials property of azobenzene-functionalized polypeptides upon UV irradiation [105–107]. It will be interesting to incorporate this chemistry in the design of light-responsive, polypeptide-based DDSs in the future.

3. Release of payloads through the change in drug-polypeptide interactions

In addition to the physical entrapment, another common strategy to load therapeutic agents is the formation of chemical bonds between drugs and polymers, followed by the assembly of the drug/polymer complexes. The application of stimuli disrupted the drug-polymer interactions, leading to the disassembly of the complexes and the release of the payloads. Common drug-polymer interactions include covalent conjugation, charged interaction, metal complexation, and donor-acceptor coordination. With the versatile side-chain designs [22],

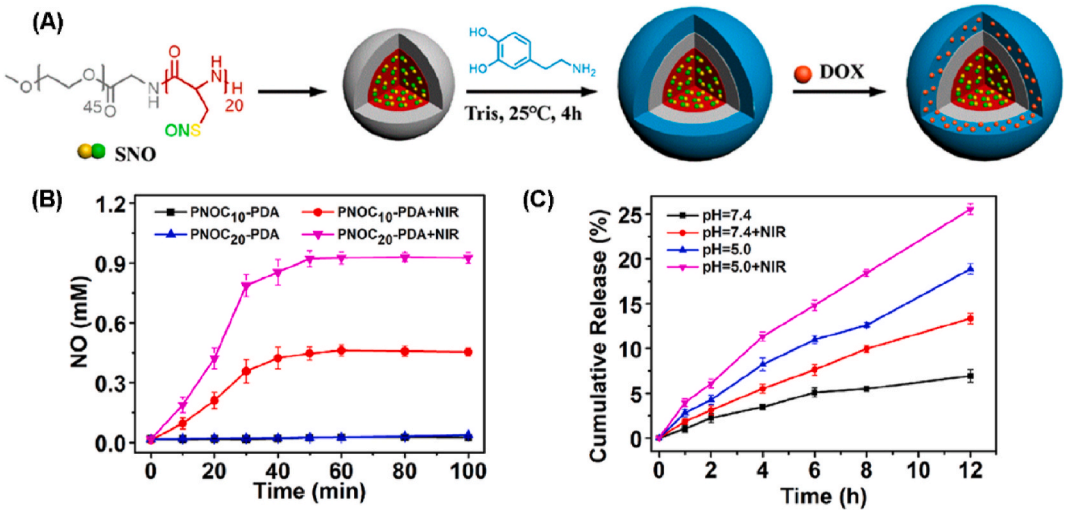


Fig. 7. Light-responsive assemblies with polypeptide-based NO gas therapy. (A) Scheme illustrating the preparation of PNOC-based micelles for synergistic triple therapies. (B) NIR-dependent release of NO from PNOC. (C) NIR- and acid-triggered release of DOX from PNOC-based micelles. Reprinted with permission from Ref. [104]. Copyright 2019 American Chemical Society.

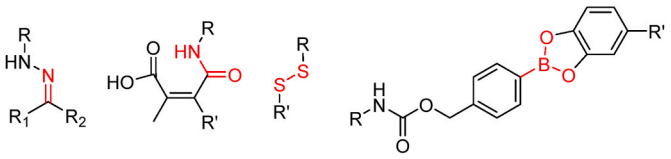
various functionalities were attached onto polypeptides for stimuli-responsiveness as well as drug incorporation.

In this section, we will review several polypeptide-based DDSs with various trigger-responsive drug-polypeptide interactions (Table 1). The materials design and the fine tuning of release behavior will be discussed, which may provide new insights in the future development of stimuli-responsive DDSs.

3.1. Disruption of drug-polypeptide covalent conjugations

The side-chain carboxylic acid groups from PAsp and PLG segments serve as the conjugating sites to react with the amino or hydroxyl groups from small-molecular drugs [108,109]. Up to now, the first generation of polymeric micelles are in clinical development (*e.g.*, NK-911, NK-012, NC-6301) [110–113]. These micelles are fabricated through the conjugation of anticancer drugs onto polypeptide side chains through amide or ester bonds. Meanwhile, a growing number of polypeptide-drug conjugates, such as CT-2103 and CT-2106, have been evaluated in different phases of clinical trials to treat unspecified adult solid tumor [114–117]. Nevertheless, the release of these conjugated drugs relies on the hydrolysis of drug-polypeptide linkages that is difficult to control. Additionally, a series of polypeptide-drug conjugates were developed based on PLL dendrimer and various drugs, where the linker between the drug and the polypeptide plays an important role in tuning the release of the drug [118].

To control the release of drugs from polypeptide-drug conjugates, small-molecular drugs were conjugated onto polypeptide side chains through trigger-cleavable linkages, which releases the free drugs upon stimuli. For instance, Kataoka and co-workers reported the conjugation of DOX onto the polypeptide side chain of PEG-*b*-PAsp through a pH-sensitive hydrazone linkage (Scheme 7) [119]. The conjugated DOX turned the polypeptide segments hydrophobic, which induced the assembly of the copolymers into micelles. The acidic environment in



Scheme 7. Chemical structures of stimuli-responsive linkages involved in polypeptide-drug conjugates. The trigger-responsive cleavable sites are highlighted in red.

Table 1
Summary of polypeptide-based DDSs with trigger-responsive change in drug-polypeptide interactions.

Drug-polypeptide interactions	Strategies for cargo release	Functionality for drug-polypeptide interactions	Cargo[a]	Functionality for programmed release	Refs
Covalent conjugation	Cleavage of linkers between drug and polypeptide	–	DOX, EPI, WOR, DEX, MG132	Hydrazone	[119–135]
			siRNA	Maleic amide	[136]
			CPT, siRNA, GEM	Disulfide	[137–139]
			RNase A	phenyl borate	[142]
Columb interactions	(De)protonation of polypeptides or drugs	Charged groups	DOX, MEL, MTO	Carboxylic acid	[150–158]
	Elimination of charged residues on polypeptides		DNA, siRNA, Pt(IV)	Ketal, disulfide, and phosphonic acid	[159–161]
	Charge conversion		DNA, siRNA, lysozyme, cytochrome, IgG, DOX, CDDP	Maleic amide, zwitterions	[162–173]
Metal complexation	Ligand substitution under physiological conditions	Carboxylic acid	CDDP, DACHPt	–	[174–185]
Donor-acceptor coordination	Disruption of the coordination	Phenylboronic acid	DOX, EPI, IR, Volasertib	–	[186–188]

[a] DOX = doxorubicin, EPI = epirubicin, WOR = wortnammin, DEX = dexamethasone, MG132 = Cbz-leu-leu-leucinal, CPT = camptothecin, GEM = gemcitabine, RNase A = ribonuclease A, MEL = melittin, MTO = mitoxantrone, IgG = immunoglobulin G, CDDP = *cis*-dichlorodiamino platinum(II), DACHPt = dichloro(1,2-diaminocyclohexane)platinum(II), IR = irinotecan.

endolysosomes triggered the cleavage of the hydrazone bond that disrupted the micelles and released the free DOX. For clinical evaluations, DOX was replaced with epirubicin (EPI), a derivative with lower cardiotoxicity and similar efficacy [120–122]. The acid-sensitive formulation (NC-6300) based on EPI has entered phase I clinical trials to investigate its safety, tolerability, and recommended dosage, and to determine the efficacy of NC-6300 in patients suffering from advanced or metastatic solid tumors. The advance of NC-6300 indicates an exciting move of the second generation of polypeptide-drug conjugates from bench to bedside. Additionally, the nano-assemblies from drug-conjugated copolymers were further used as the carriers for free hydrophobic drugs [123,124]. For instance, Kataoka, Cabral, and co-workers reported the preparation of polypeptide-based micelles for the eradication of cancer stem cells [123]. EPI was conjugated onto PEG-*b*-PAsp through hydrazone linkages, which was then used to load a protein kinase inhibitor, staurosporine (STS). The affinity between two drugs not only help the loading of STS in the micelle core, but also synchronize the release of both drugs under acidic conditions.

In addition to the pH-sensitive hydrazone linkage [119,125–135], acid-labile maleic amide linkage [136] and redox-responsive disulfide linkage [137–139] were also used to trigger intracellular release of conjugated drugs (Scheme 7). The latter linker was designed as the intracellular concentration of glutathione (GSH, 0.5–10 mM) is much higher than the extracellular concentration (2–20 μM) [140,141]. Cargos other than chemotherapeutic drugs, such as small-interfering RNA (siRNA), were also conjugated to facilitate their selective intracellular delivery.

Chen, Xiao, and co-workers reported the preparation of a polypeptide-based DDS that enables the co-delivery of proteins and DOX [142]. Specifically, a polypeptide-based triblock copolymer was synthesized, whose second and third block was modified with catechol and tertiary amine, respectively. DOX was first loaded into the micelles during the assembly of the triblock copolymer, which was further stabilized by the addition of a phenylboronic-acid-modified RNase A through the formation of phenyl borate (Scheme 7). Upon cell entry, the decrease in pH resulted in the cleavage of phenol borate linkage and facilitated the release of DOX. DOX-induced cell apoptosis led to the increase of ROS levels, which further triggered the degradation of phenylboronic acid linker and the unmasking of RNase A.

3.2. Disruption of drug-polypeptide charged interactions

Charged polypeptides have been extensively used to form complexes with other charged molecules through Coulolumb interactions [35]. For instance, the formation of polyion complex (PIC) micelles were observed by mixing PEG-*b*-PAsp with a negatively charged polypeptide segment and PEG-*b*-PLL bearing a positively charged polypeptide block [143]. When one of the charged molecules are therapeutic agents, the resulting drug/polypeptide charged complex was studied as promising DDSs. Cationic polypeptides have been widely used for gene delivery; PLL is one of the first cationic polymers used for DNA complexation [144]. Later developments of PEG-*b*-poly(*N*-aspartamide) [145,146] and α-helical, cationic polypeptides [147–149] offer promising non-viral vectors for the delivery of DNA and siRNA. While beyond the scope of the current paper, we recommend the authors to refer to some nice reviews summarizing the progress of polypeptide-based gene delivery [5,11,46].

The pH-responsive deprotonation/protonation of anionic polypeptide segments, such as PLG, provide facile loading/release of cationic drugs. Instead of using neutral DOX, charged DOX (*i.e.*, DOX·HCl) formed complexes with copolymers bearing PLG block [150–156] (Fig. 8A and B), where higher drug loading was observed compared with the physical encapsulation method with DOX [150]. Compared with temperature, the aqueous pH exhibited a more significant impact on the release of DOX·HCl from PLG-based assemblies due to the enhanced hydrophilicity of DOX under acidic conditions (Fig. 8C). Chen group reported nearly 100% loading efficiency of DOX·HCl using PEG-*b*-PLG, which was attributed to not only the charge complexation between DOX·HCl and PLG but also the hydrophobic stacking between DOX·HCl [151]. The same lab further optimized the copolymer structure for better performance, by introducing hydrophobic PPhe segments into the polypeptide block to enhance the stability of the micelles [153]. In addition to the complexation between DOX·HCl and PLG, pH-responsive DDSs with other ionic drugs and charged polypeptide segments were also developed [157,158].

Stimuli-responsive elimination of charged residues is another common strategy to release the cargos from drug/polypeptide complexes. Through incorporation of trigger-responsive linkers onto polypeptide side chains, charged residues were cleaved upon the application of triggers, which disrupted the drug-polypeptide interactions, leading to

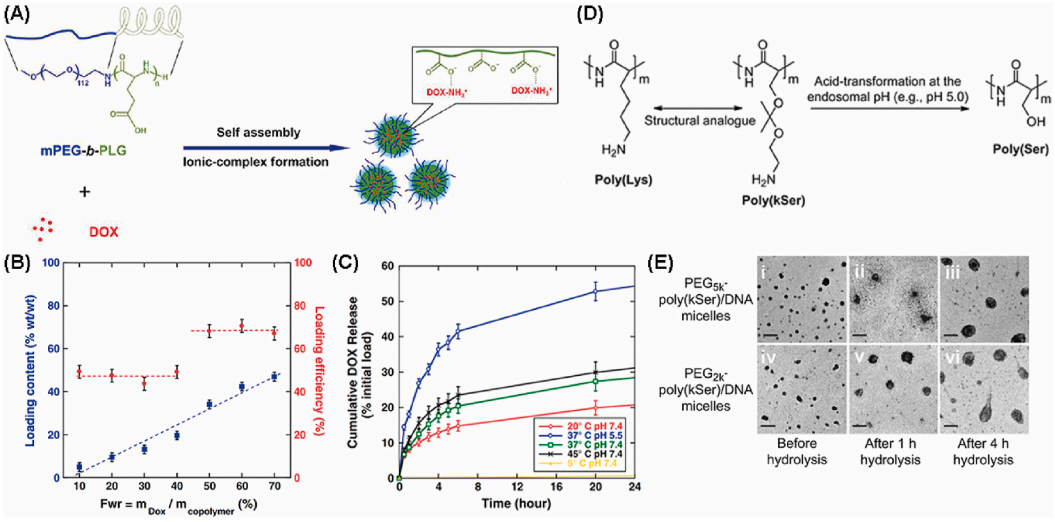
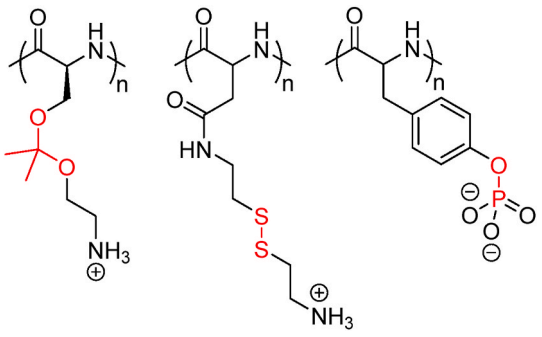


Fig. 8. Disruption of drug-polypeptide charged interactions. (A) Scheme illustrating the loading of DOX·HCl with PLG-based polymers. Reprinted with permission from Ref. [151]. Copyright 2013 American Chemical Society. (B) The loading content and loading efficiencies of DOX·HCl with PLG-based copolymers through nanoprecipitation. (C) pH-dependent release profile of DOX·HCl from PLG-based micelles. Reprinted with permission from Ref. [150]. Copyright 2010 Elsevier. (D) Chemical structure of PLL-mimicking Poly(KSer) and the pH-triggered side-chain cleavage. (E) TEM images of PEG-*b*-poly(kSer)/DNA complexes before and after hydrolysis at acidic pH. Scale bar = 200 nm. Reprinted with permission from Ref. [159]. Copyright 2010 Elsevier.

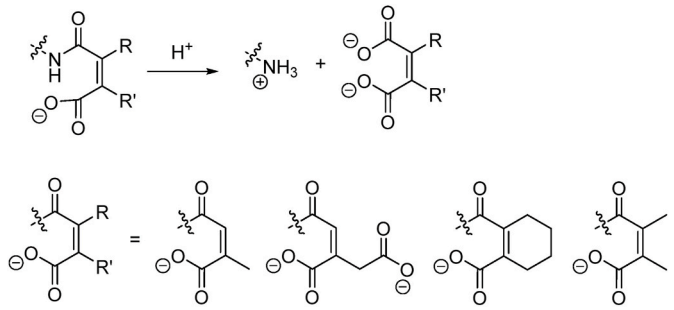
the controlled release of the payloads. For example, Kwon and co-workers reported the use of pH-responsive copolymer, PEG-*b*-poly (kSer) (Scheme 8 and Fig. 8D), as non-viral gene delivery vectors for triggered release of DNA inside cells [159]. The side-chain ketal linkers were cleaved in acidic endosomes, disrupting the complexes and facilitating the release of DNA cargos (Fig. 8E). In a similar approach, redox-responsive disulfide groups were introduced on polypeptide side-chains (Scheme 8), whose cleavage under high intracellular GSH environment triggered the release of complexed siRNA [160]. The strategy was also used to remove the anionic groups on PEG-*b*-poly ($_{L}$-phosphotyrosine) (PEG-*b*-PpY) in the presence of alkaline phosphatase (ALP) (Scheme 8), promoting the release of positively charged, Pt (IV)-based prodrug [161].

In an attempt to further promote the release of cargos from drug/polypeptide complexes, charge-conversional moieties were introduced onto either drugs or polypeptide side chains. Maleic amide derivatives are widely used as charge-conversional units (Scheme 9), which degrade at acidic pH and expose the protected amino groups. With the acid-triggered charge-conversion property, maleic amide derivatives were included in membrane-active polypeptides, polypeptide/DNA complexes or polypeptide-drug conjugates to facilitate the endosome escape through the "proton-sponge" effect [137,162–164]. In addition, maleic amide derivatives were also used to promote the release of cargos from drug/polypeptide PIC micelles. For instance, Kataoka group reported the preparation of stable PIC micelle between positive lysozyme and block copolymer with an anionic polypeptide segment [165]. The side chain of polypeptide was functionalized with citraconic amide, which underwent charge-conversion to expose positive charges at pH 5.5. As a result, the release of lysozyme was facilitated through the charge repulsion with the new, positively-charged poly(*N*-aspartamide) block (Fig. 9A and B). The same lab also used this strategy to modify the protein cargos at the lysine residues, which was then complexed with cationic polypeptide segments for the pH-sensitive cytoplasmic protein delivery [166,167]. In a similar approach, the maleic amide derivatives was used to modify DOX·HCl or cationic polypeptides for the enhanced intracellular release of small-molecular drugs [168,169]. In addition to the maleic amide chemistry, charge conversion was also achieved by the use of zwitterionic polypeptides [170–172], whose transition pH depends on the specific fractions of cationic and anionic polypeptide residues.

The change in charged status of side chains may also alter the secondary structure of polypeptides [7]. Cheng and co-workers designed an α-helical copolypeptide as a smart non-viral gene delivery vector, which contains positively charged residues and light-responsive, masked PLG residues [173] (Fig. 9C). The copolypeptide efficiently condense with DNA and deliver DNA cargos into cytoplasm through helix-specific cell penetration mechanism. Upon light irradiation, the exposure of negative PLG charges not only weakened DNA-polypeptide interactions, but also disrupted the helical conformation, therefore promoting the release of DNA and reducing helix-associated toxicity (Fig. 9D and E).



Scheme 8. Chemical structures of representative polypeptides bearing stimuli-responsive linkages for the elimination of charges.



Scheme 9. Chemical structures of maleic amide derivatives with acid-triggered charge conversion property.

3.3. Disruption of other drug-polypeptide interactions

Polypeptide-based copolymers containing carboxylic acid side chains, like PAsp [174] and PLG [175–182], are intensively studied as carriers for Pt(II) drug, an important class of antitumor agents. Commonly used copolymers include block copolymers or graft copolymers of PLG with PEG, *i.e.*, PEG-*b*-PLG and PLG-*g*-PLG. The platinum drugs were released from these carriers in a slow and sustained manner under physiological conditions, due to the ligand substitution with chloride anions (Fig. 10A). Polypeptide-based formulation consisting of PEG-*b*-PLG and *cis*-dichlorodiamino platinum(II) (CDDP) (NC-6004) has entered phase III clinical trials to determine their efficacy, in combination with gemcitabine *vs* gemcitabine alone, in patients with locally advanced or metastatic pancreatic cancer [183,184]. Encouraged by the clinical results of NC-6004, PEG-*b*-PLG incorporating dichloro(1, 2-diaminocyclohexane)platinum(II) (DACHPt) (NC-4016) was proposed to enhance the therapy efficacy and reduce the side effects, which also started its Phase I clinical trial in November 2013 [185]. In addition, Kataoka, Nishiyama, and co-workers reported an interesting phenomenon that the release of CDDP was dependent on the chirality of poly(glutamic acid) block, offering an interesting strategy to tune the drug release through secondary structure control [179]. The formation of α-helical bundles was observed when PEG-*b*-PLG was used to complex CDDP, resulting in higher stability and sustained release of drugs. In contrast, CDDP-loaded micelles with copolymers bearing racemic poly ($_{D,L}$-glutamic acid) segments showed lower stability and accelerated release.

Donor-acceptor coordination was also used in polypeptide-based DDSs [186–188]. Yin and co-workers reported polypeptide-based micelles with high loading (~50%) and nearly quantitative loading efficiency (>95%), which was attributed to the nitrogen-boron (N–B) coordination interactions between drug and polypeptide side chains (Fig. 10B) [186]. The PBA moieties on polypeptide side chains provide electron-accepting sites, which form strong coordination interactions with the amine group on various drugs. Both the oxidation of PBA under ROS conditions and the protonation of DOX at low pH disrupted of the N–B coordination, resulting in selective release of coordinated cargos. The donor-acceptor coordination interactions provide an alternative for selectively drug release in response to specific stimulus in target sites.

The use of PBA unit was not limited to design glucose-responsive vehicles and drug carriers with N–B coordination interactions. Kataoka group reported the preparation of ATP-responsive DDSs using PBA-modified polypeptide segments [189]. The PBA units stabilized the siRNA complexes by interacting with the *cis*-diols on the ribose ring. Under high concentration of ATP, which also has ribose moieties, fast release of encapsulated siRNA was observed due to the competitive binding interactions (Fig. 10C).

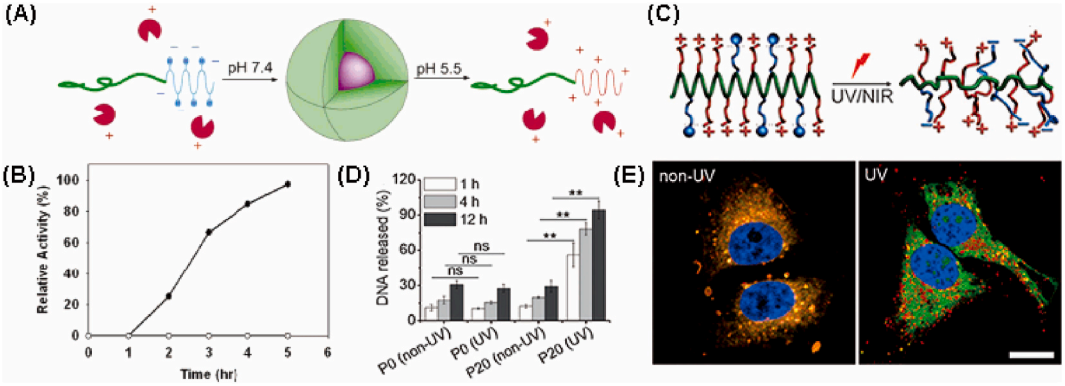


Fig. 9. Cargo release facilitated by charge conversion strategy. (A) Scheme illustrating the assembly/disassembly of the PIC micelles from lysozyme and polypeptide-based copolymers bearing charge-conversional moieties. (B) The relative lysozyme activity from the charge-conversional PIC micelles at pH 5.5 (solid symbols) and pH 7.4 (open symbols). Reprinted with permission from Ref. [165]. Copyright 2007 American Chemical Society. (C) Schematic illustration of light-triggered structural change of helical polypeptides. UV light changed the charged status of the polypeptides that facilitated the unpacking of DNA. (D) The release of DNA cargos from non-treated and UV-treated complexes based on UV-responsive polypeptides P20. P0 with no UV-responsive segments were used as control group. (E) Confocal images revealing the successful unpacking of DNA (green) from the polypeptide vectors (red) after UV irradiation. Scale bar = 20 mm. Reprinted with permission from Ref. [173]. Copyright 2013 John Wiley and Sons. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

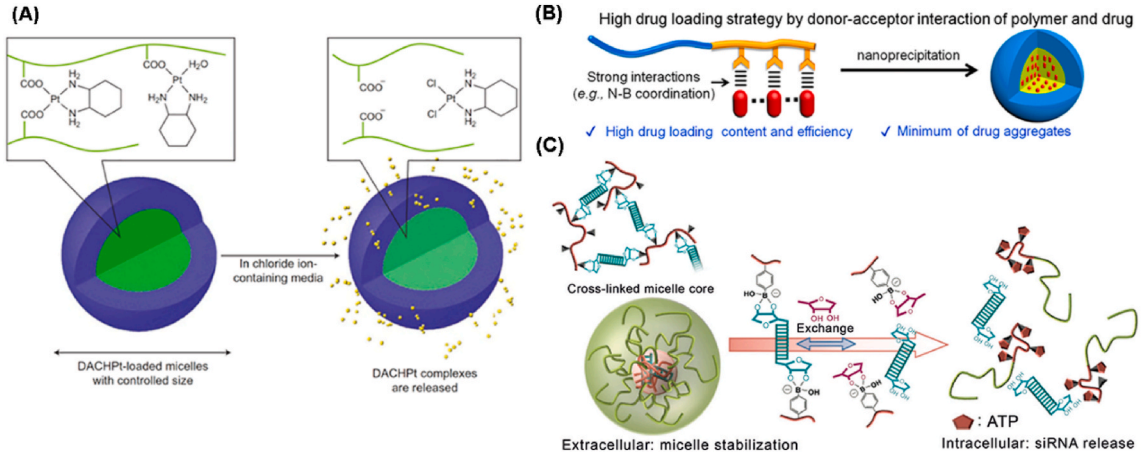


Fig. 10. Disruption of drug-polypeptide metal complexation and donor-acceptor coordinations. (A) Scheme illustrating the release of Pt(II) drugs from polypeptide-based PIC micelles through ligand exchange. Reprinted with permission from Ref. [176]. Copyright 2011 Springer Nature. (B) Scheme showing the N–B coordination interactions between drugs and polypeptides. Reprinted with permission from Ref. [186]. Copyright 2018 American Chemical Society. (C) Schematic representation of the PBA-based strategy for siRNA delivery with ATP-triggered release behavior. Reprinted with permission from Ref. [189]. Copyright 2012 John Wiley and Sons.

4. Other release strategies

4.1. Degradation of polymer backbones

Polypeptides synthesized from NCA ROP, especially those with natural amino acid residues, have shown satisfactory backbone degradation rate in the presence of proteolytic enzymes. Early studies revealed that the incorporation of hydrophobic, less sterically-hindered amino acid residues, such as L-alanine, resulted in faster enzymatic degradation [190,191].

With these understandings, poly(L-alanine) (PAla) was widely used to render polypeptide-based hydrogels and nano-assemblies enzyme-degradable [192–194]. For instance, Jeong and co-workers evaluated the stability of PEG-*b*-(PAla-*co*-Phe) hydrogel in the presence of various proteolytic enzymes, which showed significant degradation after a 3-d incubation (Fig. 11A) [192]. In contrast, the hydrogel showed good stability in PBS in the absence of enzymes (Fig. 11B). Rapid enzyme degradation was also reported for PLL-*co*-PLG hydrogels [195]. Additionally, polypeptide hydrogels based on modified natural amino acid residues and non-natural amino acid residues, such as poly (γ-ethyl-L-glutamate) and poly(α-aminopalmitic acid), were readily degraded in the presence of enzymes [196–198]. These hydrogels showed promising results for sustained delivery of anticancer drugs.

Zhong, Deng, and co-workers reported the preparation of enzyme-responsive PEG-*b*-poly(L-tyrosine) (PEG-*b*-PTyr) for the delivery of DOX [199]. PEG-*b*-PTyr nanoparticles exhibited ultra-high loading of DOX because of the strong π-π stacking between PTyr side chains and the drug. Due to the rapid degradation of the PTyr segments in the presence of proteinase K, enzyme-responsive release of the encapsulated DOX was observed (Fig. 11C and D). The same research group further modified the nano-assemblies with targeting ligands, which showed improved selectivity towards cancer cells compared with the non-targeted analogues [200,201].

Besides the degradation of polypeptide segments, cleavable linker was also introduced into polypeptide-based, amphiphilic block copolymers. The trigger-responsive cleavage of the linker altered the assembly behavior and facilitate the release of encapsulated cargos. For instance, various PEG-*b*-polypeptides bearing disulfide linkages between the PEG and polypeptide blocks were synthesized using disulfide-containing PEG macroinitiators [202–207]. The detachment of PEG

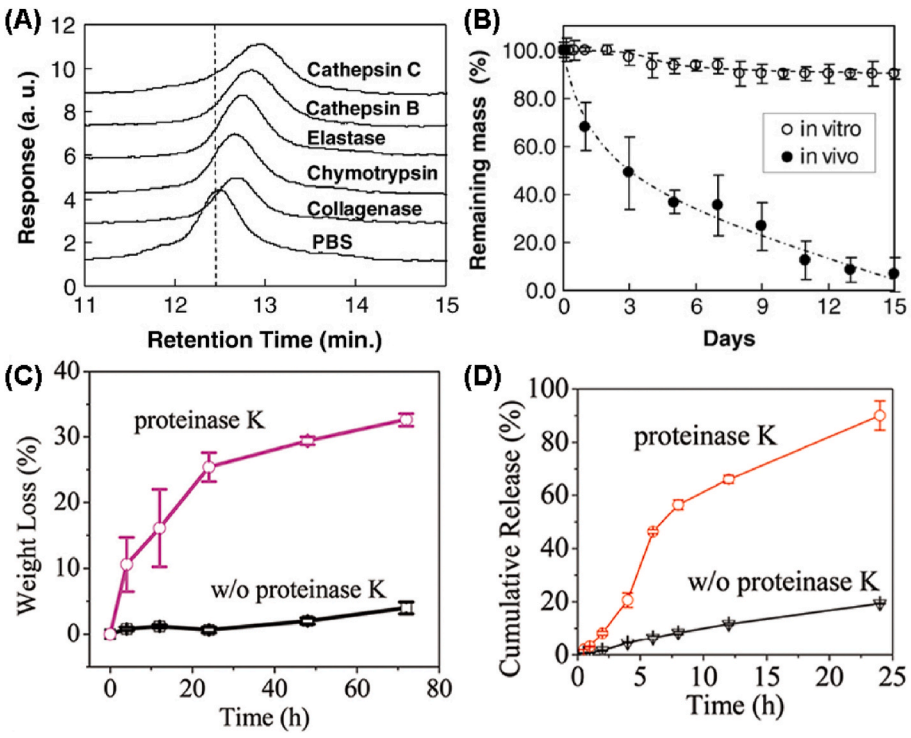


Fig. 11. Degradation of polypeptide backbones catalyzed by proteolytic enzymes. (A) Degradation of PEG-*b*-(PAla-*co*-Phe) in the presence of various proteolytic enzymes. PBS treatment was used as the control group. (B) Mass loss of PEG-*b*-(PAla-*co*-Phe) gel in PBS without proteases (in vitro) and in the rats with proteases (*in vivo*). Reprinted with permission from Ref. [192]. Copyright 2009 Elsevier. (C) Weight loss of the PEG-*b*-PTyr films with or without proteinase K. (D) Release of DOX from PEG-*b*-PTyr nanoparticles in the presence or absence of proteinase K. Reprinted with permission from Ref. [199]. Copyright 2018 Royal Society of Chemistry.

under reductive conditions destabilized the nano-assemblies, resulting in the rapid release of DNA (Fig. 12A and B) or small-molecular drugs (Fig. 12C and D). With a similar strategy, disulfide was installed as the linker of other polypeptide-based assemblies, whose reductive-responsive cleavage resulted in the disruption of the nanoparticle and the rapid release of payloads [208,209]. Additionally, pH-responsive maleic amide linker was also incorporated between PEG and polypeptide blocks for acid-triggered disassembly [210].

4.2. Cleavage of crosslinkers

Crosslinking is a powerful strategy to stabilize drug-loaded carriers and prevent the premature release of cargos [211,212]. The use of trigger-sensitive crosslinkers enables the destabilization of carriers and release of payloads at targeted sites. Specifically, disulfide crosslinkers are widely used in polypeptide-based DDSs due to their ease of installation and rapid cleavage in cancer cells. Disulfide was introduced into polypeptide-based carriers through the oxidation of side-chain thiols [210,213–222], the exchange of side-chain disulfides [200,223–226], the addition of disulfide-containing crosslinkers [227–230], and the direct polymerization of L-cystine NCA dimer [231–238]. Among these methods, the use of L-cystine NCA provides a facile strategy to generate redox-responsive nano-assemblies in one pot [231,233]. In addition, the core functionalization through unreacted pendent NCAs further broadened the scope of the method (Fig. 13).

In addition to the disulfides, other trigger-sensitive crosslinkers were also included in the polypeptide-based DDSs, including ROS-responsive diselenides [239], pH-responsive ketals [240], and glucose- or ATP-responsive PBA/sugar units [241–244]. For instance, the glucose-responsive nano-assemblies were prepared either through the mixing of PBA- and glucosamine-functionalized polymers [241,243], or by crosslinking the glycopolypeptide-based copolymer with a

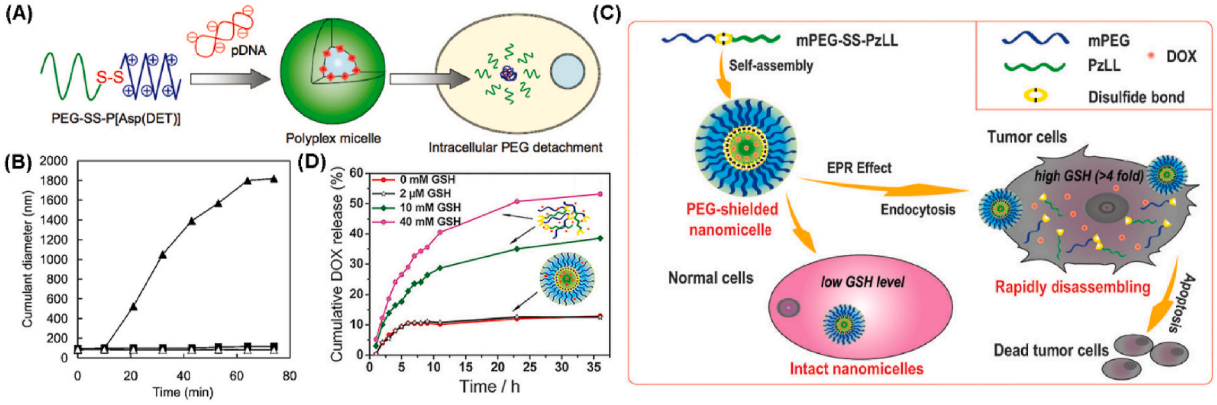


Fig. 12. Degradation of polymer backbones through trigger-cleavable linkers. (A) Schematic illustration of PEG-detachable PIC micelles and the intracellular PEG detachment. (B) The change in the size of PIC micelles with high (10 mM, solid triangles) and low (10 μM, open triangles) concentration of DTT. PIC micelles without PEG-detachment design was used as the control group (open squares). Reprinted with permission from Ref. [202]. Copyright 2008 American Chemical Society. (C) Scheme showing PEG-detachable nanomicelles for redox-sensitive release of DOX. (D) Release of DOX from nanomicelles in the presence of various concentration of GSH. Reprinted with permission from Ref. [204]. Copyright 2011 Royal Society of Chemistry.

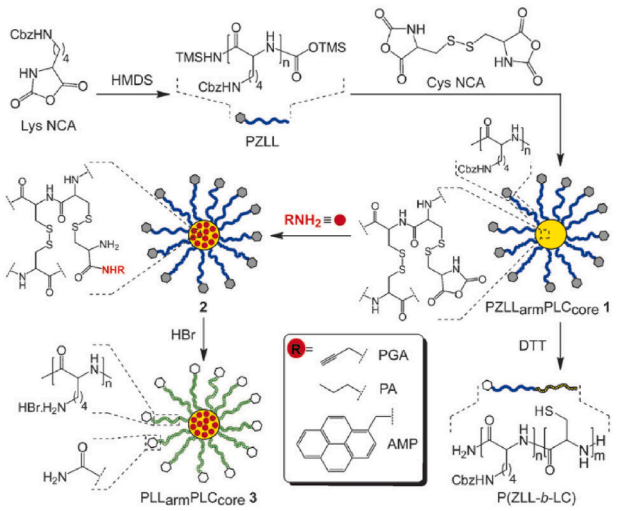


Fig. 13. Synthesis route to core cross-linked polypeptide nanoparticles using L-cystine NCA. Reprinted with permission from Ref. [231]. Copyright 2011 Royal Society of Chemistry.

bifunctional PBA linker [242]. The resulting carriers serve as promising vehicles for the delivery of insulin.

5. Conclusion and perspectives

Nature uses the 21 amino acids as the building blocks for the construction of proteins, the life-essential structural and functional materials. Based on these amino acids and coupled with the use of other non-peptidyl materials, essentially unlimited polypeptide biomaterials are achievable with rich structures, conformations and functionalities for drug delivery application. As highlighted in this review, advances in strategies for controlled-release of payloads in polypeptide-based DDSs have led to exciting progress in nanomedicine-based therapeutics and diagnosis in the past decades. Researchers have built an expansive toolbox to fabricate polypeptide-based vehicles with unique properties that are non-achievable in other biopolymer-based DDSs.

Despite these exciting advances, challenges remain in polypeptide-based DDSs. While peptides or proteins are remarkably successful when used as standalone therapeutics, with majority of the blockbuster drugs in the past 20 years are protein-based [245], the achievement of using polypeptides as drug delivery vehicles has been limited. Given the rich functionality of polypeptides, it is natural that focuses have been largely on designing various chemistries for trigger-responsive release of payloads from the polypeptide-based delivery vehicles. However, more evidences of clinical applications are essential for the translational development of the polypeptide-based DDSs. Polypeptide clearly has the advantage over many other materials for its functional, conformational, and structural versatility. However, its drawbacks are also obvious. Compared with natural proteins, synthetic polypeptides are heterogeneous materials with polydisperse molecular weight distribution and poor control over monomer sequence for copolypeptides. In polypeptide-drug conjugates with lack of control over drug conjugation site, the heterogeneity of the materials and its impact on the *in vivo* use in the clinical and translational research should be put into consideration for further improvement. Many of the reported polypeptide DDSs, although showing remarkable control over triggered release, have limited studies on the impact of materials heterogeneity on the efficiency of drug delivery.

Synthetic polypeptides used in drug delivery are almost exclusively derived from the ROP of NCA. Efforts to improve the synthesis of polypeptides have been continuous in the past few decades, including some of the most recent advances on accelerated polymerization [246–253], open-air polypeptide synthesis [248,254–256], and the direct polymerization of non-purified monomers [254,257]. These new chemistries, particularly with the advent of bench-top synthesis of the polypeptides circumventing the use of complicated apparatus such as glovebox and Schlenk techniques, may further expand the use of polypeptide materials in drug delivery. The direct preparation of polypeptide nanoparticles from NCA monomers, including branched polypeptides as unimolecular micelles [247,258–261] and polymerization-induced self-assemblies (PISA) [256,262], opens new possibility to generate polypeptide-based nanocarriers in one step. Another interesting trend in polypeptide biomaterials area is the use of the unique secondary structure of polypeptide for the benefit of drug delivery and controlled release. While the synthetic polypeptides with built-in stable secondary structure have shown remarkable biological activities [147,179,263], the study for the use of secondary structure in drug delivery has been limited, and its unique benefit is yet to be demonstrated. Polypeptides, as the analogue of protein, the very few life-essential polymeric materials (other than DNA, polysaccharides), clearly have competitive advantages over many other synthetic polymeric materials in drug delivery. With the new advances in materials preparation, novel materials design, and the versatile strategy for programmed drug release, we expect to see tremendous opportunities of polypeptide-based materials in drug delivery and controlled release applications.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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