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Mini-Review

Recent Advances in Photo-Responsive Polypeptide Derived Nano-assemblies

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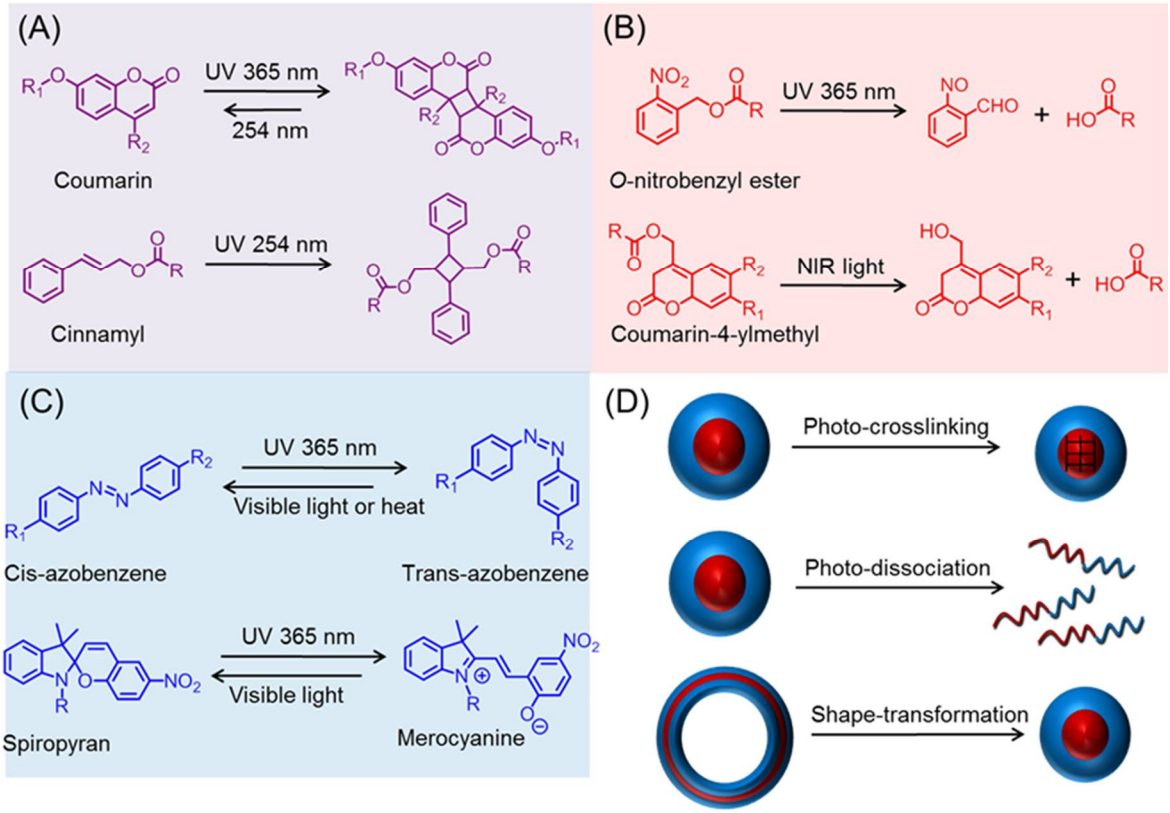
Abstract: Stimuli-responsive polymeric materials have attracted significant attentions in a variety of high-value-added and industrial applications during the past decade. Among various stimuli, light is of particular interest as a stimulus due to its unique advantages such as precisely spatiotemporal control, mild conditions, ease of use, and tunability. In recent years, a lot of effort toward synthesis of biocompatible and biodegradable polypeptide has resulted in many examples of photo-responsive nanoparticles. Depending on the specific photochemistry, those polypeptide derived nano-assemblies are capable of crosslinking, disassembling, or morphing into other shapes upon light irradiation. In this mini-review, we aim to assess the current state of photo-responsive polypeptide based nanomaterials. First, those "smart" nanomaterials will be categorized by their photo-triggered events (i.e., crosslinking, degradation, and isomerization) which are inherently governed by photo-sensitive functionalities including *o*-nitrobenzyl, coumarin, azobenzene, cinnamyl, and spiropyran. In addition, the properties and applications of those polypeptide nanomaterials will be highlighted as well. Finally, the current challenges and future directions of this subject will be evaluated.

Keywords: Stimuli-responsive polymers; synthetic polypeptide; photo-sensitive; self-assembly; Morphological transformation

1. Introduction

Stimuli-responsive or "Smart" polymers are capable of changing their physical and/or chemical properties upon receiving external triggers such as temperature, pH, redox, mechanical forces, and light.[1-9] These tailor-made polymers are receiving significant interests in the fields of drug delivery, biosensor, tissue engineering, coatings, and self-healing materials.[10-14] In particular, light has recently garnered tremendous attention as a stimulus since it can be not only triggered externally but also provides spatiotemporal control.[15-23] Moreover, irradiation parameters including wavelength, power, and time can be easily tuned to fit the system (e.g., on-demand and controllable drug release rate).[24-27] Typically, the ability of smart polymers to response to light stems from the incorporation of photo-sensitive chemical structures.[28-30] Those moieties can be classified into three general categories based on their specific photo-chemistry (Scheme 1). In the first category represented by cinnamyl and coumarin, photo-induced dimerization of those groups takes place upon irradiation at a certain wavelength while the dimer can undergo reversal reaction at another wavelength with a higher energy (i.e., shorter wavelength). The second (e.g., *o*-nitrobenzyl) involves irreversible photo-triggered degradation, which can liberate the unprotected functionality, leading to dramatic change in solvability. The last subset includes functional groups such as azobenzene and spiropyran that are capable of reversibly isomerizing under different wavelengths.

Scheme 1. Photo-chemistry of various functional groups. (A) UV-induced dimerization; (B) UV or NIR promoted cleavage; (C) Reversible isomerization by UV and visible light; (D) Photo-triggered metamorphosis of polypeptide derived nano-objects.



Inspired by natural protein, synthetic polypeptides or poly(amino acids) based nanomaterials are receiving increasing interests in the field of polymer science due to their inherent biocompatibility and biodegradability.[31,32] Furthermore, synthetic polypeptides have exhibited their unique ability to form higher order secondary structures including α-helix, β-sheet, and β-turn thanks to non-covalent interactions (i.e., hydrogen bonds, pi-pi stacking, and hydrophobic interaction) between amino acids side chains.[33,34] Those non-covalent interactions are highly sensitive to local environments such as temperature, pH, the presence and concentration of reducing agent, ionic strength, and even light. A small change in local environment could have noticeable impact on non-covalent interactions, resulting in transformation of secondary structures and concomitant change in bio-activity and function of polypeptides.[35]

The rapid development of polymerization methodology has empowered polymer chemists with the ability to easily prepare unique polypeptides with diverse architecture and functionalities.[36-39] Numerous polypeptides have been successfully prepared via various living polymerization approaches such as ring-opening polymerization of *N*-carboxyanhydrides (NCA),[40-43] reversible addition-fragmentation polymerization,[38] atom transfer radical polymerization,[44,45] and ring-opening metathesis polymerization.[46-50] In typical case, living or controlled polymerization techniques are capable of producing polymers with precise chain lengths, excellent functionalities tolerance, and narrow polydispersity.[51-55] In addition, complicated architectures such as block, cyclic, brush, and star which were previously inaccessible can be now easily made via living polymerization techniques.[56-64] Owing to those features arising from living polymerizations (vide supra), one can design and tune the hydrophobic to hydrophilic balance, which dictates the critical packing parameters and give rise to nanoparticles with predictable morphologies (Scheme 2).

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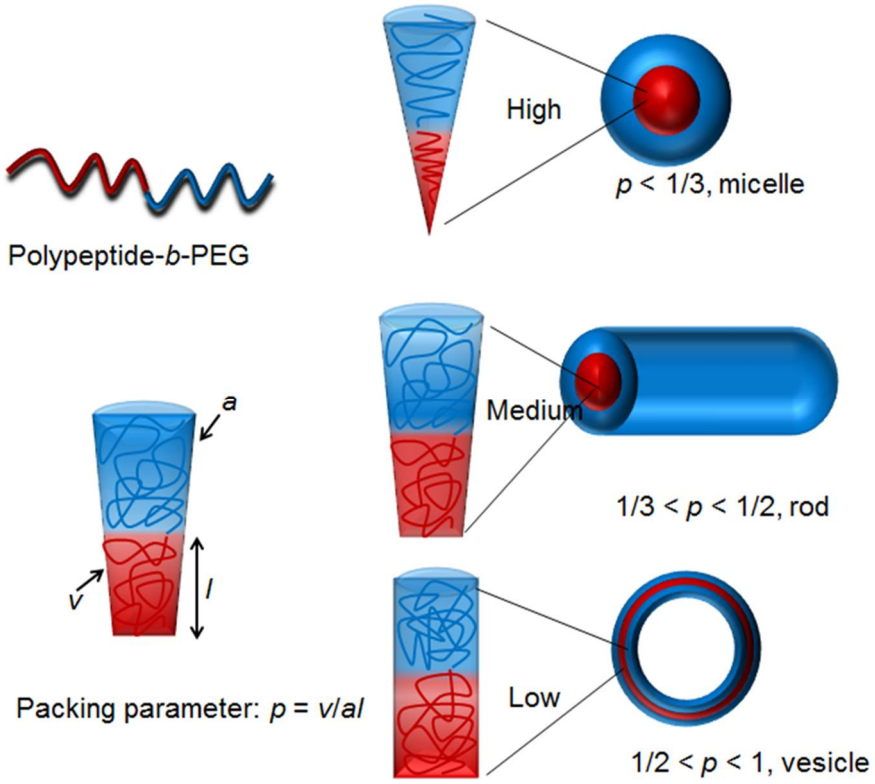
Scheme 2. The shapes of polypeptide derived nano-objects are dictated by critical packing parameters. Diblock copolymer polypeptide-*b*-PEG exemplifies amphiphilic polypeptide based copolymers.



With the recent success of light-responsive amphiphilic polypeptides in nanotechnology and nanomedicine, we believe it is necessary to assess the current state of those smart nanomaterials. In this mini-review, main focus will be placed on photo-chemistry of various light-sensitive functional groups that are incorporated into the polypeptide nanoparticles. Furthermore, we will discuss the influence on size or morphologies of nano-assemblies as a consequence of light treatment and how this may assist prediction of potential applications of those materials. Finally, we believe it is crucial to evaluate the current challenges and future directions of this field.

2. Photo-chemistry of light-responsive polypeptide nanoparticles

2.1. Photo-crosslinkable nanoparticles

Photo-dimerizable or crosslinkable groups including cinnamic, coumarin, and anthracene can undergo a crosslinking reaction via [2+2] cycloaddition of the carbon-carbon double bonds after UV-irradiation.[65-67] They have been mainly utilized for photo-crosslinking of micelles, leading to micelles or nanogels with enhanced colloidal stability even in very dilute condition.[68-70] Compared with traditional crosslinking methods such as “click” chemistry and carbodiimide coupling, photo-crosslinking approach is relatively inexpensive, rapid, and highly efficient at room temperature. Furthermore, no byproduct is generated during photo-dimerization process, rendering the final product with high purity. [71]

Chen et al. demonstrated the first example of photo-crosslinkable polypeptide based micelle.[72] In their work, diblock copolymer poly(ethylene glycol)-*b*-poly(L-glutamic acid) was synthesized by ring-opening polymerization (ROP) of L-glutamate-NCA monomer in the presence of PEG-amine macroinitiator. The resulting diblock copolymer further underwent deprotection and subsequent modification with cinnamyl alcohol, yielding amphiphilic PEG-*b*-polypeptide containing pendent

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cinnamyl functionalities. Core-shell micellar structure was formed by self-assembly of PEG-*b*-polypeptide into water. Moreover, UV-irradiation at 254 nm led to photo-crosslinking of the micellar core, which was directly proven by dynamic light scattering (DLS) showing a decreased size of nanoparticle after core-crosslinking. Jing and coworkers reported the synthesis and ROP of a functional NCA monomer bearing a cinnamyl moiety.[73] Water soluble PEG-amine macroinitiator was utilized during polymerization process, leading to well-defined PEG-*b*-polypeptide copolymers which possess cinnamyl groups in the side chains of hydrophobic polypeptide. The block copolymer was capable of self-assembling into micelles that can be core-crosslinked under UV light (Figure 1). It is noteworthy to mention that jing's direct polymerization approach achieved full functionalization of cinnamyl in the repeating units of polypeptide chain. However, in the case of Chen's post-modification modification method, only partial functionalization of repeating units with cinnamyl can be realized due to low efficiency of esterification under steric environment of the polypeptide.

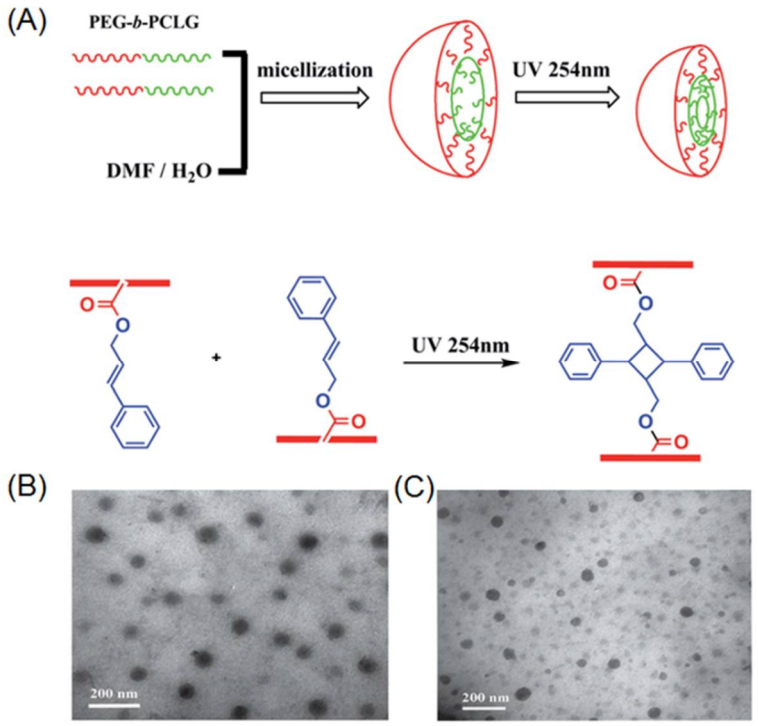

Figure 1. (A) Self-assembly of PEG-*b*-polypeptide and subsequent photo-induced core-crosslinking;(B) TEM image before UV irradiation; (C) TEM image after UV irradiation[73], Copyright 2012. Reproduced with permission from the Royal Society of Chemistry.

Beyond cinnamyl photo-chemistry, coumarin based reversible dimerization has also been illustrated in the fabrication of photo-crosslinkable polypeptide micelles. In a pioneering work by Luo, solution-phase peptide synthesis was employed to obtain a linear-dendritic block copolymer composed of hydrophilic PEG (5 KDa) and hydrophobic branched polylysine containing peripheral coumarin groups (Figure 2).[74] Since the block copolymer is amphiphilic, micellar nanoparticles were observed in water. When long-wavelength UV irradiation (>310 nm) was applied to micelle solutions, core–crosslinking event was rapidly completed within 400 seconds as indicated by UV-Vis spectra. More interestingly, photo-induced decrosslinking occurred upon exposure to a short wavelength UV light (254 nm), elucidating the reversibility of this process. Notably, decrosslinking reaction of coumarin dimer underwent a significantly slower kinetics (over 100 min) compared with that of crosslinking process.

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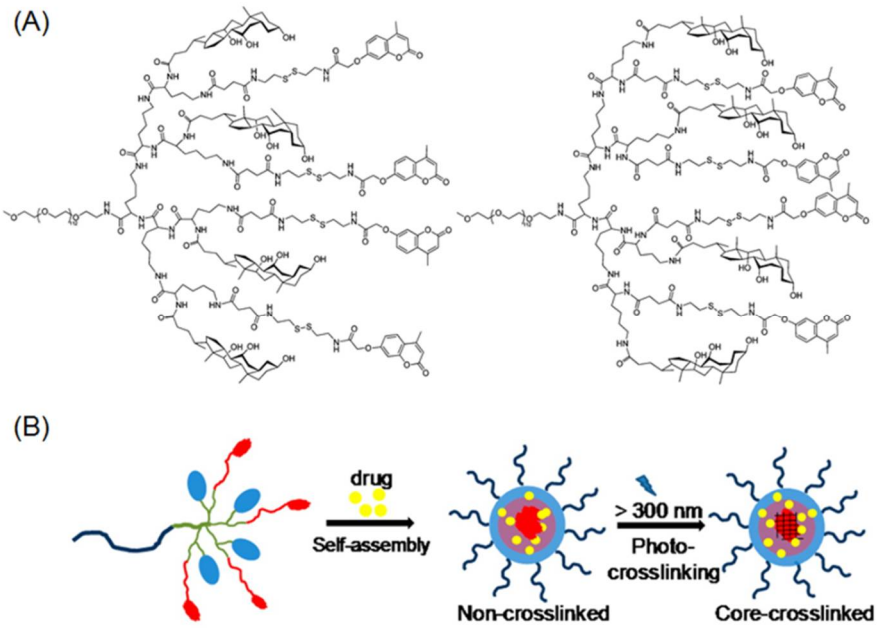

Figure 2. (A) Chemical structures of linear-dendritic PEG-*b*-polylysine containing coumarin moieties at their periphery; (B) light-triggered photo crosslinking of drug-loaded micelles [74], Copyright 2014. Adapted with the permission from the American Chemical Society.

2.2. Photo-cleavable nano-objects

While polypeptide derived diblock copolymer micelles can acquire enhanced stability through photo-crosslinking process, the concern regarding lack of degradability still remains especially in biomedical applications.[75,76] In view of this, photo-cleavage chemistry has emerged as an alternative approach to photo-sensitive polypeptide nanoparticles.[13,77-82] More importantly, photo-cleavage reactions are typically accompanied by dramatic increase in water-solubility of hydrophobic segment, which could promote either disassembly or morphological transformation of nano-objects.

Several illustrative examples of photo-cleavable polypeptide nanoparticles involving *o*-nitrobenzyl groups have been reported by Dong et al. In their first work, a photo-sensitive *S*-(*o*-nitrobenzyl)-L-cysteine NCA monomer (abbreviated as NBC) was designed and polymerized with PEG-amine as macroinitiator, giving rise to diblock copolymer PNBC-*b*-PEG.[79] Since NBC repeating units are hydrophobic due to the presense of *o*-nitrobenzyl moieties in the side chains, the amphiphilic block copolymer is able to form micelles with a size of 79 nm. This approach conferred photo-degradability to the micelles because the hydrophobic core consists of numerous UV-labile *o*-nitrobenzyl groups. Transmission electron microscopy (TEM) and dynamic light scattering demonstrated that the block copolymer micelles were capable of dissociating into smaller nanoparticles (44 nm) upon UV irradiation at 365 nm. The reduction in particle size is due to photo-cleavage of *o*-nitrobenzyl groups, producing free thiols with enhanced water solubility. A later report described photo-induced shape transformation of polypeptide-containing vesicles (Figure 3).[81] In that work, $PNBC_{56}$-*b*-PEG_{114} (the subscript represents the number of repeating units) was synthesized and used for constructing vesicle morphology in aqueous solution. The vesicle solution was subsequently exposed to 365 nm UV light, promoting the cleavage of *o*-nitrobenzyl groups and concomitant increment in hydrophilicity of PNBC block. As the ratio of hydrophilicity to hydrophobicity increased, critical packing parameters of the nano-assemblies decreased, inducing morphological transition from vesicle to micelles. In addition, free thiol inside the micellar core can be further oxidized in the presence of an oxidizer (i.e., hydrogen peroxide), resulting in formation of disulfide linkages which prompt aggregation of the micelles.

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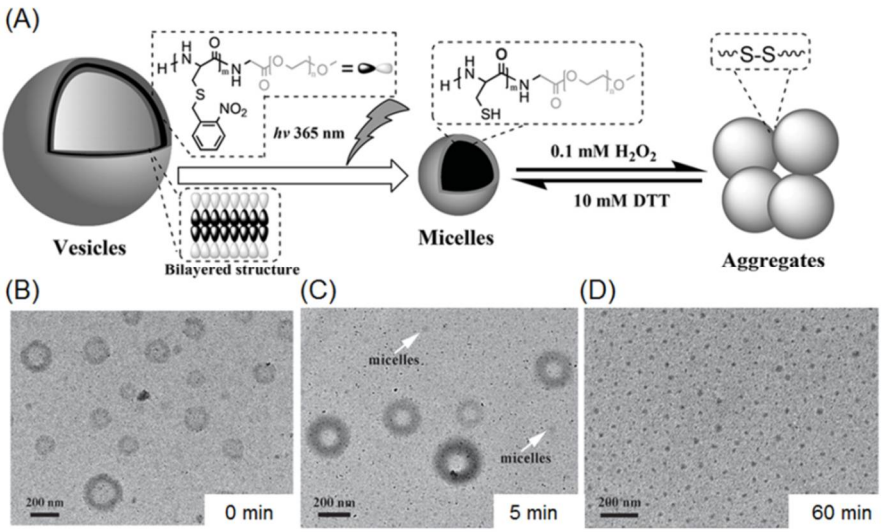

Figure 3. (A) Shape programming of polypeptide based nanoparticles through photo-regulation and redox process; (B) Vesicular structures before UV treatment; (C) A mixture of vesicles and micelles after UV irradiation for 5 mintes; (D) After UV-irradiation for 1 hour, vesicles were fully transformed to micelles[81], Copyright 2014. Adapted with the permission from John Wiley and Sons.

Very recently, the same group invented NIR-responsive PNBC-*b*-PEG upconversion composite micelles (Figure 4).[13] During the block copolymer self-assembly process, upconversion nanoparticles (UCNP) were encapsulated inside the PNBC core. The composite micelles were capable of disassembling with the help of UCNP converting NIR light (980 nm) to UV light (365 nm). Moreover, Zhao and coworkers reported a novel NIR light-sensitive micellar system based on a diblock copolymer consisting of PEG and poly(L-glutamic acid) bearing pendent 6-bromo-7-hydroxycoumarin-4-ylmethyl groups, an efficient NIR two-photon-absorbing chromophore (Figure 5).[77] Upon irradiation with 794 nm NIR light, the chromophores were gradually removed from polypeptide chain, shifting the hydrophilic-hydrophobic balance toward disassembly of micelles in water. Notably, nearly 200 minutes of irradiation was needed to fully cleave the side chain groups, demonstrating the potential of controlled release kinetics.

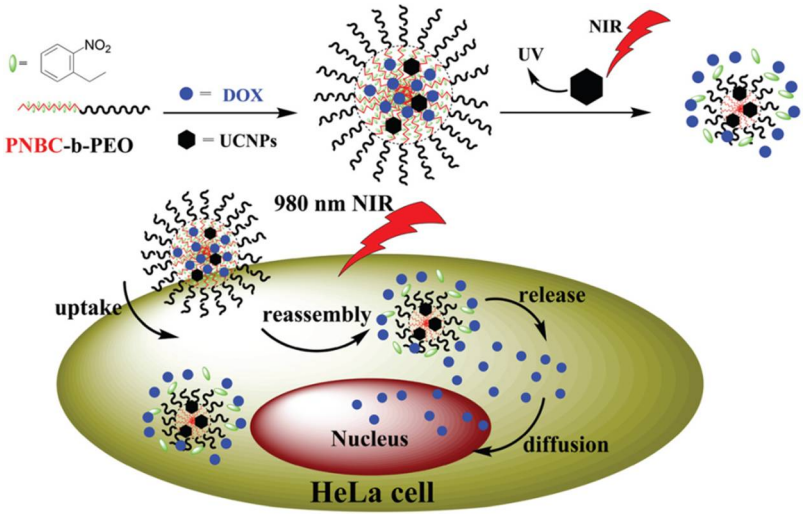

Figure 4. Fabrication of NIR-responsive polypeptide micelles via encapsulation of UCNP into block copolymer micellar core. Upon NIR irradiation, UCNP converts NIR into UV light, which further cleaves *o*-nitrobenzyl moieties and induces disassembly of micelles[13], Copyright 2015. Reproduced with permission from the Royal Society of Chemistry.

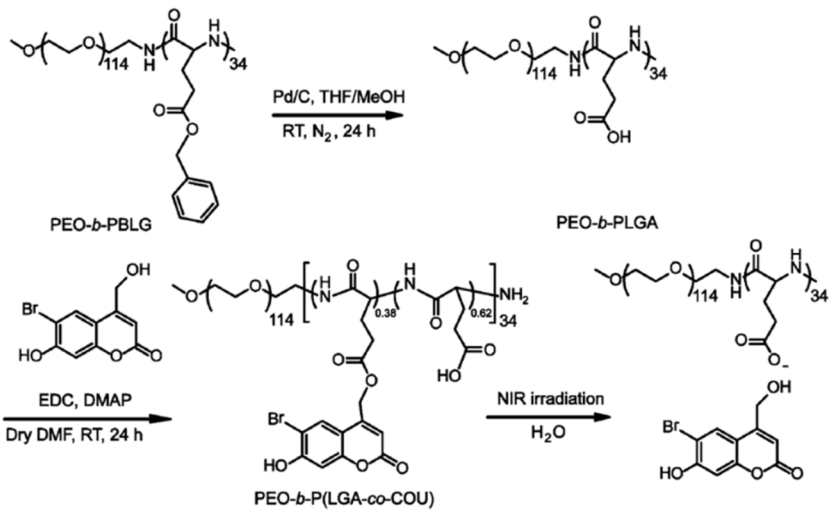

Figure 5. Synthetic route to NIR-responsive diblock copolymer consisting of PEG and polypeptide bearing coumarin groups[77], Copyright 2012. Reproduced with permission from the Royal Society of Chemistry.

2.3. Photo-isomerizable nano-assemblies

According to the properties of aforementioned photo-crosslinkable and photo-cleavable polypeptide nanoparticles (vide supra), we can easily draw the conclusion that photo-induced shape transformation or micellar disruption based on those functionalities are non-reversible under common conditions. While de-crosslinking reaction of coumarin dimer can be literally achieved, the condition (i.e., 254 nm) is harsh and the slow reaction could cause decomposition of coumarin and lead to undesired side reactions.[83] In the case of *o*-nitrobenzyl, UV-induced photo-redox cleavage would generate *o*-nitrosobenzaldehyde that cannot reform the original o-nitrobenzyl moiety. To further pursue efficient and reversible photo-responsiveness of polypeptide nano-assemblies, some research groups have designed smart nanoparticle systems which relies on photo-isomerizable functionalites such as azobenzene and spiropyran.[40,84-90]

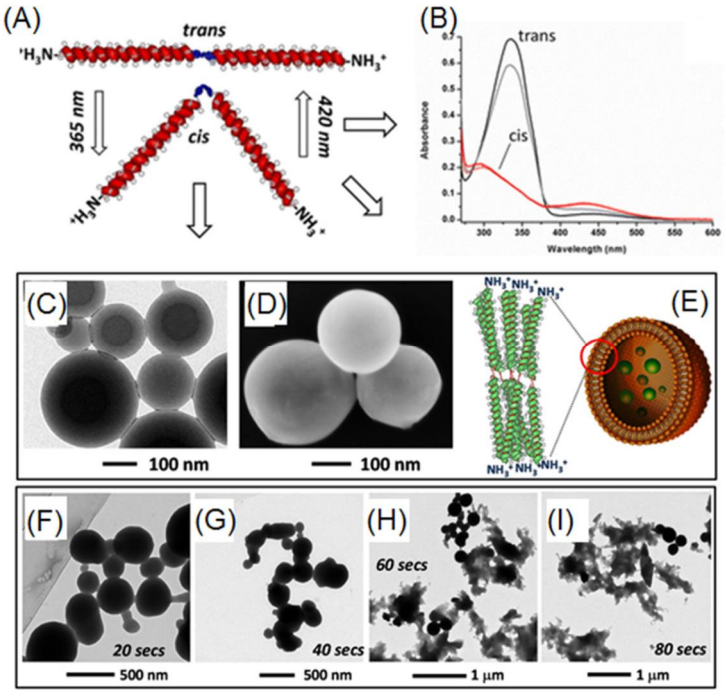

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Figure 6. (A) Reversible geometry change of azobenzene-containing polypeptide via UV and visible light; (B) UV-Vis absorptions of cis- and trans-isomers; (C) and (D) TEM and SEM images of vesicles arising from self-assembly of trans-isomer of polypeptides; (E) Cartoon representation of vesicular structure based on trans-polypeptide; (F-I) Time-dependent UV-induced degradation of vesicles[89], Copyright 2014. Adapted with the permission from the American Chemical Society.

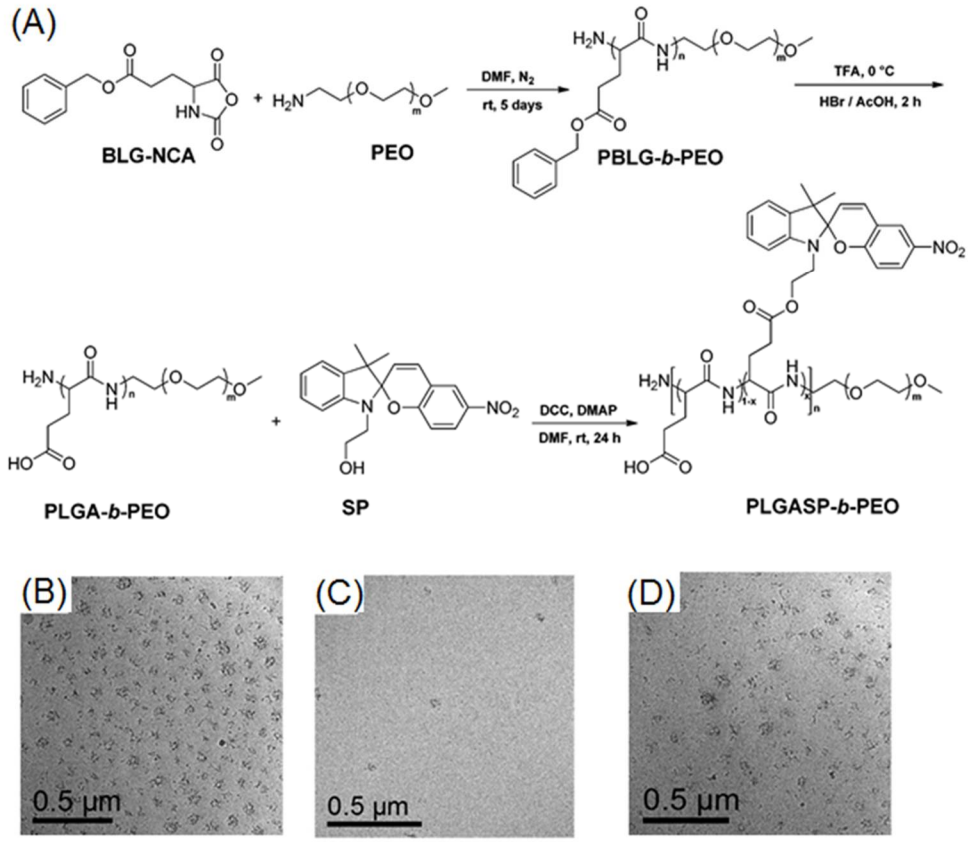

Figure 7. (A) Synthetic route to spiropyran-bearing polypeptide-*b*-PEG diblock copolymer; (B) TEM image of polymer nano-objects before UV treatment; (C) TEM image after UV irradiation; (D) TEM image of regenerated micelles after applying visible light to UV-treated polymer solution[91], Copyright 2017. Reproduced with permission from the Royal Society of Chemistry.

Azobenzene is capable of transitioning between two isomers (i.e., cis and trans) through manipulation of UV light (365 nm) and visible light. When UV light is present, polar cis-isomer is favorably formed. On the other hand, visible light or heat can promote the shift of isomerization towards thermodynamically favored non-polar trans-isomer. To date, azobenzene derivatives have been extensively incorporated into many peptides, either in the side chains or in the backbone. In a report by Moretto, azobenzene served as a central linker for diblock poly(γ-benzyl-L-glutamate) (PBLG).[89] Before UV irradiation, diblock PBLG trans-isomer nanoparticles as evidenced by TEM (Figure 6). After exposure to UV light, a rapid and gradual collapse of those ordered vesicles was observed probably owing to trans-to-cis azobenzene transformation which induced change in 3D geometry of diblock polypeptide. Lu and coworkers were able to synthesize photo-responsive polypeptides via ROP of NCA monomers that consist of pendent azobenzene and oligoethylene glycol (OEG), affording P(OEG-Azo).[40] Because of the presence of both hydrophobic azobenzene and hydrophilic OEG, P(PEG-Azo) can self-assemble into nanoparticles in aqueous solution. Moreover, α-helical conformation of polypeptide was observed in the case of azobenzene trans-isomer. Upon UV treatments, trans-cis isomerization occurred and forced polypeptides to adopt a disordered conformation as evidenced by circular dichroism spectroscopy. Importantly, reversible conformation switch was found when heating the UV-treated cis-polypeptides at 70°C.

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Spiropyran (SP) is a widely-used photochromic molecule thanks to light-induced spiropyran-to-merocyanine (SP-MC) isomerization.[92,93] Original SP derivatives are in their closed form, appearing as colorless, nonpolar, and hydrophobic compounds. Isomerization toward MC (open form) occurred under UV treatment, leading to MC derivatives which are colored, polar, and hydrophilic. Mezzenga et al. presented an excellent example of photo-reversible micelle system based on spiropyran-containing polypeptide-*b*-PEG diblock copolymer (Figure 7).[91] First, they performed kinetic study of SP-MC and MC-SP isomerization using UV-Vis spectroscopy. Before UV irradiation (365 nm), the solution was colorless suggesting the absence of MC form. After UV irradiation, the absorption peak at 544 nm progressively increased and reached maximum value within 5 minutes, indicative of fast and complete SP-MC isomerization. Nevertheless, MC-SP isomerization happened much slower and reached full conversion after 180 min in the presence of visible light (590 nm). After demonstrating photo-regulated reversibility of SP-PC isomerization, the authors further utilized TEM to observe reversible aggregation-dissolution-aggregation process of block copolymers in water. According to their results, original SP isomer containing polymers were capable of self-assembling into micelles. UV irradiation fully disrupted the micellar structure after 5 min because of the formation of hydrophilic MC moieties. Interestingly, micelles were successfully recovered as a consequence of visible light treatment for 3 hours.

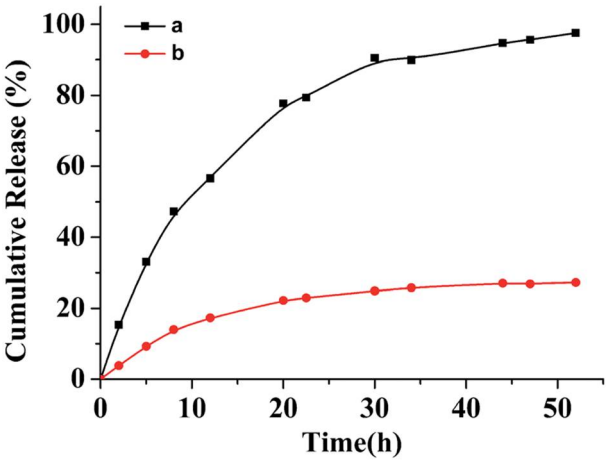

Figure 8. Cumulative release of drugs from non-crosslinked polypeptide micelle (black square) and photo-crosslinked polypeptide micelle (red dot)[73], Copyright 2012. Reproduced with permission from the Royal Society of Chemistry.

3. Properties and applications

Apparently, polypeptide derived nanoparticles hold a great potential to serve as excellent drug delivery systems due to their biocompatibility and biodegradability. Moreover, aforementioned photo-chemistry confers those nanoparticles with attractive properties such as enhanced colloidal stability and on-demand drug release. Jing and coworkers investigated *in vitro* paclitaxel (PTX) release from two batches of PTX-loaded peptide micelles with one batch treated with UV light.[73] According to their result, the drug release from crosslinked micelles was significantly slower than that from non-crosslinked micelle. For instance, only 20% of the drug was leaked from crosslinked micelle during 55 hours incubation in PBS buffer while almost 100% drug was released from non-crosslinked micelle under same condition (Figure 8). In Zhao's study, NIR-responsive Rifampicin-encapsulated polypeptide micelles showed neglectable release after 55 hours in the absence of NIR irradiation. When NIR laser was turned on, progressive drug release was observed, demonstrating the feasibility of this drug delivery system to achieve on-demand drug release.

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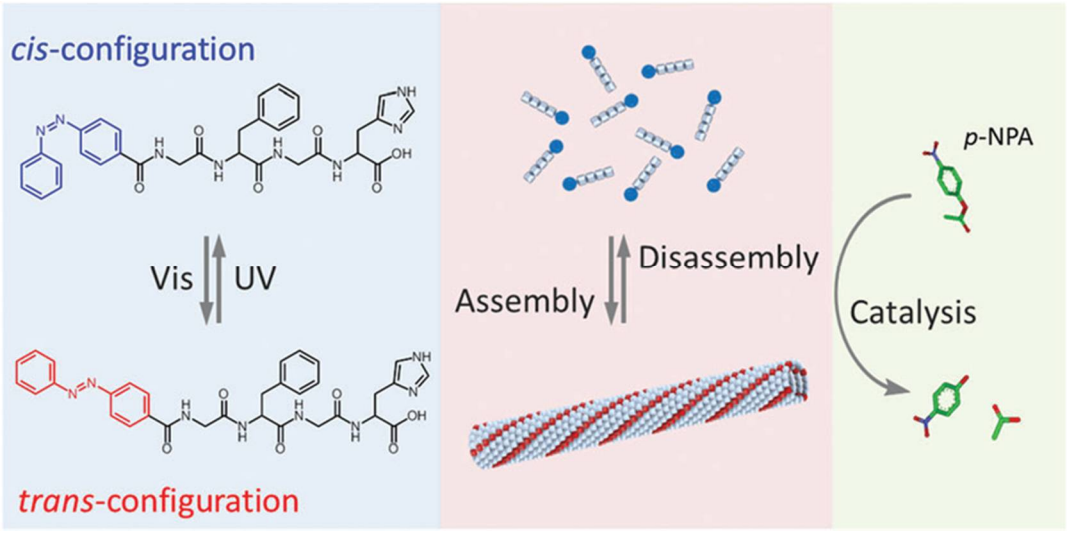

Figure 9. Molecular structures of azobenzene-terminated peptide and photo-switchable assembly and catalytic activities of the peptide based artificial hydrolase[86], Copyright 2018. Reproduced with permission from the Royal Society of Chemistry.

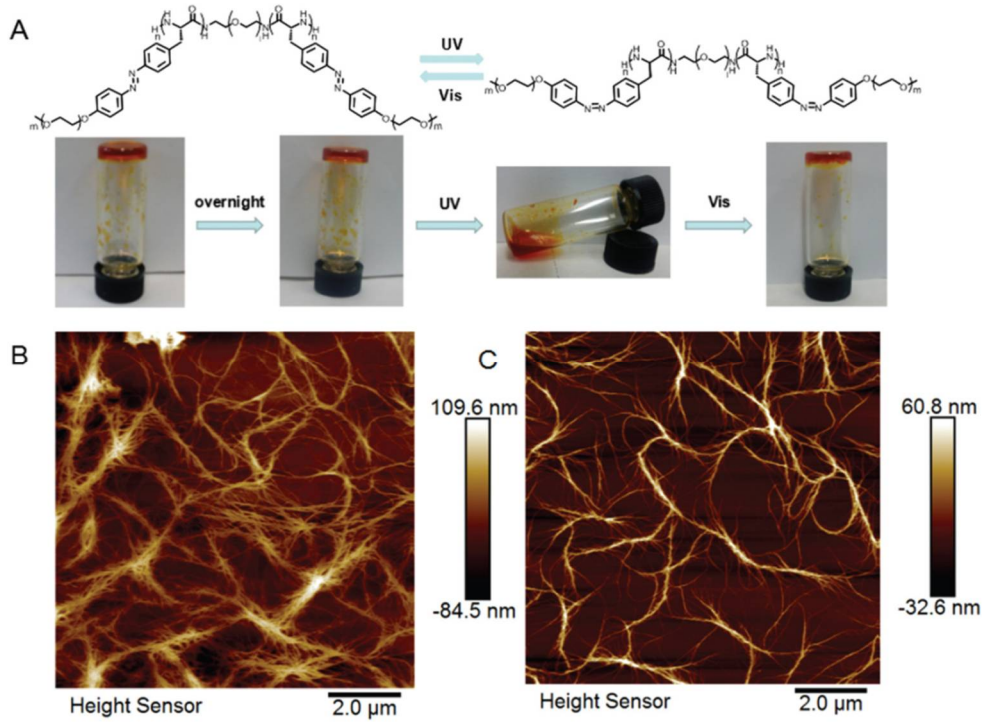

Figure 10. (A) Reversible sol-gel process by switching light wavelength between UV and visible; (B) AFM image of polymer solution before UV treatment; (C) AFM image of polymer solution after UV irradiation[40], Copyright 2016. Reproduced with the permission from the Royal Society of Chemistry.

In addition to biomedical applications, photo-responsive polypeptides have been used in the field of catalysis as well. He and coworkers designed a peptide-based artificial hydrolase which consists of a catalytic histidine residue and a photo-responsive azobenzene group in the peptide chain (Figure 9).[86] Before UV irradiation, the peptide exhibits an antiparallel β-sheet conformation, enabling self-assembly into peptide fibril. An enhanced catalytic activity on *p*-nitrophenyl acetate was observed because of the hydrophobic environment of peptide fibril and proximity effect of histidine groups. However, a significant reduction in catalytic efficiency occurred upon exposure to

UV-light, which caused conformational conversion of peptide from β-sheet to random coil and thus disrupted supramolecular fibril structure. Most importantly, the authors were able to demonstrate that the activity of peptide-based artificial hydrolase can be reversibly controlled by using visible and UV light.

Finally, the application of photo-sensitive polypeptides was successfully translated into macroscopic materials involving reversible sol-gel process as described by Hu and Li (Figure 10).[40] In their study, an organogel was formulated by dissolving azo-bearing polypeptide-*b*-PEG-*b*-polypeptide triblock copolymer in THF. Interestingly, the gel was capable of switching physical states between gel and solution upon alternating visible and UV treatment. According to atom force microscope images, the gel revealed a densely crosslinked fibrous network while the solution exhibited a much smaller degree of crosslinking after UV irradiation.

4. Current challenges and prospective

Many relatively recent developments in photo-responsive polypeptides have greatly expanded the scope of smart nanomaterials, providing us with many new possibilities and opportunities in various applications such as drug delivery, self-healing materials, and catalysis. Indeed, the marriage of polypeptide and photo-chemistry not only confer biocompatibility to the nanomaterials but also facilitate the structural control of peptide chains or nano-assemblies due to the ease of using light. In view of photo-chemistry relying on different light-sensitive functionalities, a number of photo-sensitive peptide nanoparticles with distinct properties have been accomplished.

Despite the tremendous success described above, many challenges still remain. One significant barrier is the translation of light-responsive polypeptide drug delivery system into clinical use. Indeed, the majority of examples in this review involve the use of UV light or visible light, which has poor penetration depth into human tissue. Moreover, UV light has been shown to be detrimental to healthy cells and tissues.[94-98] Due to those downsides of using UV/Vis light, NIR-responsive polypeptide nanoparticles represent a more promising platform for nanomedicine.[99] However, the current NIR-responsive polypeptide derived drug delivery systems suffer from either slow drug release kinetics or introduction of cytotoxic UCNP.[13,77] Therefore, more careful design and study are essential to translate those nanomaterials into biomedical applications. Moreover, photo-responsive polypeptide nano-objects have not yet been reported by means of controlled radical polymerization (CRP) and ring-opening metathesis polymerization (ROMP). Considering the robustness of CRP and ROMP techniques to prepare polymers with complex architectures and functions, we envision that one next direction on photo-responsive polypeptides will be updating the synthetic toolbox in order to achieve more sophisticated polypeptide structures. Given the considerable success of traditional stimuli-responsive materials in biomedicine and manufacturing, we believe that photo-responsive polypeptide nanomaterials will take on more important roles to next generation of supramolecular peptide nanotechnology and material science.

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