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Review Article

Peptide Self-Assembled Nanostructures for Drug Delivery Applications

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Peptide self-assembled nanostructures are very popular in many biomedical applications. Drug delivery is one of the most promising applications among them. The tremendous advantages for peptide self-assembled nanostructures include good biocompatibility, low cost, tunable bioactivity, high drug loading capacities, chemical diversity, specific targeting, and stimuli responsive drug delivery at disease sites. Peptide self-assembled nanostructures such as nanoparticles, nanotubes, nanofibers, and hydrogels have been investigated by many researchers for drug delivery applications. In this review, the underlying mechanisms for the self-assembled nanostructures based on peptides with different types and structures are introduced and discussed. Peptide self-assembled nanostructures associated promising drug delivery applications such as anticancer drug and gene drug delivery are highlighted. Furthermore, peptide self-assembled nanostructures for targeted and stimuli responsive drug delivery applications are also reviewed and discussed.

1. Introduction

Molecular self-assembly is organizing molecules into a stable and well-defined structure under equilibrium conditions through noncovalent interactions spontaneously, which is a powerful tool in the synthesis of functional nanostructures as a bottom-up fabrication method for biomedical applications [1, 2]. Self-assembly with a variety of complex nano- and microstructures is founded in nature [3–6]. Mechanisms underlying self-assembly have been applied in many areas to prepare functional materials. In most cases, a thermodynamically stable structure is formed through enthalpic and entropic interactions that involve the basic assembling units and the reacting solvent molecules [7, 8]. Electrostatic interactions, hydrophobic interactions, hydrogen bonding, π-π stacking, and so on together make sure molecules are at stable low energy levels [9]. The self-assembly process also gives the flexibility of developing many functional materials with the desired tunable properties and structures by single molecule design and fabrication [5, 10, 11].

Recently, many self-assembly nanostructures have been synthesized from biomaterials including carbohydrates, nucleic acids, and peptides to achieve a better understanding of the self-assembly mechanism and utilize them for several biomedical applications such as tissue regeneration, drug delivery, and biosensors [12–17]. Many self-assembling systems have been developed for various biomedical applications; peptide self-assembled nanostructures remain one of the most promising directions for many reasons [18]. They are easily fabricated using solid-phase peptide methods where the peptide sequence could be specifically modified at molecular levels [19]. Custom molecular structures can be designed and synthesized through tuning the peptide basic units. Naturally occurring structures occurred in proteins such as α-helices and β-sheets that can be utilized for driving the self-assembly processes [20–22]. Moreover, the self-assembly process is also very important in the functions of cell-penetrating peptides that could play an important role in delivering the drugs inside the cell membrane and transporting genes into the nucleus [23].

Peptides consisting of natural or synthetic amino acids are basic repeating units for the construction of molecular assemblies. These simple structures help us better understand the complex biological systems and underlying mechanisms. Researchers have utilized various approaches in the synthesis of peptide building units while minimizing other possible by-products [24]. To self-assemble peptides into nanostructures, there are mainly three approaches: solid-phase peptide synthesis, ring-opening polymerization, and protein engineering [25]. The solid-phase peptide synthesis is utilized to precisely control the peptide structure with short or medium sequences. Although this method has very high yield, the synthetic sequence is less than 70 amino acids [26]. Researchers have also utilized protein engineering to fabricate peptides with longer sequences and more defined structure such as collagen and silk materials through expression in bacteria [27–29]. For large-scale production of polypeptides, people have utilized ring-opening polymerization. In this method, cyclic monomers are introduced to the end of the sequences to form a longer peptide. On the other hand, a lower accuracy of the peptide primary structure than other methods such as solid-phase peptide synthesis is noticed using this method [25].

Several reviews have been focused on the morphologies, functions, or biomedical applications of peptide self-assembled nanostructures in tissue engineering rather than drug delivery applications [24, 30–32]. There is still a need for a comprehensive review on the peptide self-assembled nanostructures for drug delivery applications. In this paper, self-assembled peptide types and structures including dipeptide, cyclic peptide, amphiphilic peptide, α-helical peptide, and β-sheet peptide as basic building blocks are introduced. Meanwhile, some relevant peptide self-assembly mechanisms are also discussed. More importantly, peptide self-assembled nanostructures for anticancer drug delivery, gene drug delivery, and targeted and stimuli responsive drug delivery applications are reviewed and discussed.

2. Peptide Types and Structures for Self-Assembly

Peptides can be assembled into different nanostructures in Figure 1 including nanotubes, nanofibers, and nanovesicles based on their design and self-assembly conditions [33]. Different types and structures of peptides including dipeptides, cyclic peptides, amphiphilic peptides, α-helical peptides, and β-sheet peptides have been utilized to self-assemble into nanostructures.

2.1. Dipeptide. Recently, researchers have claimed that short peptides have the ability to self-assemble into many different nanostructures that can minimize the difficulty and cost of the fabrication process and simultaneously enhance the stability [35, 36]. Among them, dipeptide self-assembled nanostructures are investigated intensively for various biomedical applications including drug delivery. Diphenylalanine, Phe-Phe (FF), the first reported dipeptide that has been used for the self-assembly of different nanostructures, is a core motif of the amyloid-β polypeptide segment [37]. It has been recognized as the core recognition motif to drive self-assembly in Alzheimer's disease. Many studies have been carried out to self-assemble FF dipeptides into different nanostructures including nanoparticles, nanotubes, nanovesicles, and nanowires, shown in Figure 2 [34, 38–42]. FF self-assembled nanotubes have been demonstrated to be thermally stable, which is one of the most unique properties for bioinspired materials [43]. The high yield of FF dipeptides self-assembled nanotubes was achieved through vapor deposition method, which could tune the density and length of nanotubes by controlling the monomer supply [38]. FF self-assembled nanotubes were also obtained through dissolving the dipeptides in water by sonication followed by heating. Meanwhile, FF self-assembled nanowires were achieved in water at high ionic strength. Both FF dipeptides self-assembled nanotubes and nanowires are interconvertible. These two nanostructures have been studied for mechanical applications including biosensors, nanodevices, and conducting nanomaterials [44, 45].

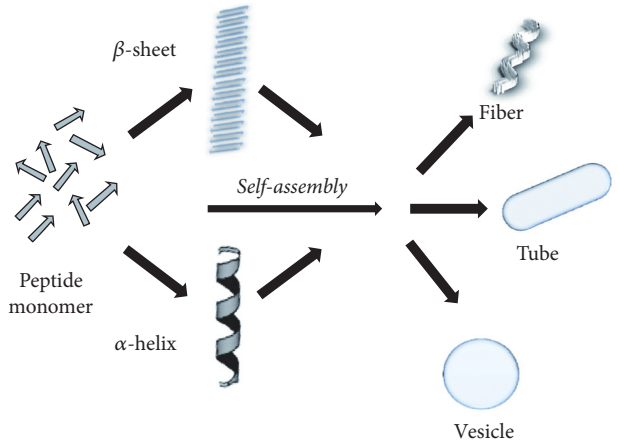

Figure 1: Peptides self-assembled into different nanostructures. Reproduced from [33] with permission from the Royal Society of Chemistry.

Hydrophobic dipeptides such as LL, LI, and LF can also self-assemble into nanotubes through hydrogen bonding. The water molecules filled nanotubes from the dipeptide WG showed negative thermal expansion, which later was utilized to form nanoporous structures from dipeptides FF, LS, IV, VI, VA, and AV [46–48]. These dipeptide self-assembled nanoporous materials have been demonstrated to absorb and store many different gasses including carbon dioxide, methane, and hydrogen [49–51]. Introducing a thiol group in FF dipeptides can change their formation from tubular to spherical nanostructures. Nanospheres, nanoplates, nanofibrils, and hydrogels were further developed from the self-assembly of several aromatic homodipeptides [52, 53]. These dipeptide self-assembled nanostructures can be applied for a casting mold to fabricate conductive nanowires and for many different biomedical applications including biosensing, tissue engineering, bioimaging, and drug delivery [53–55].

Modified dipeptides also could be used as templates for self-assembling nanostructures with tunable biological

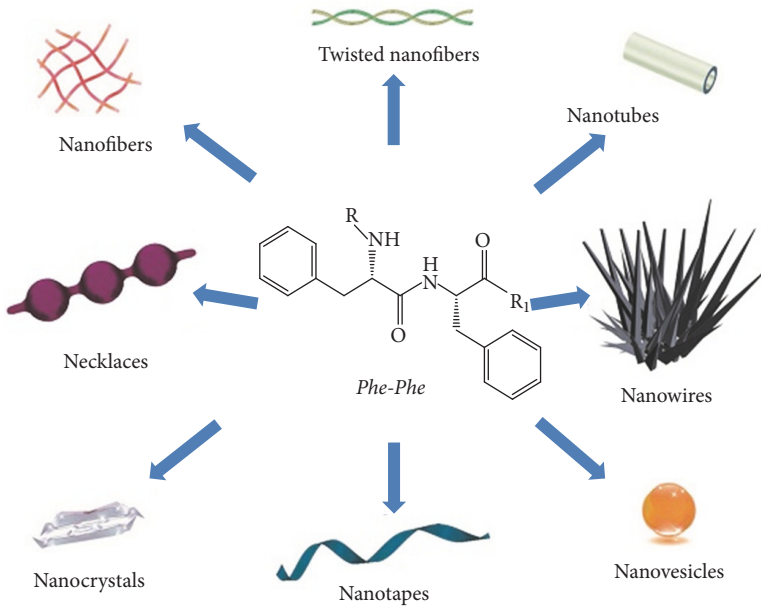

FIGURE 2: Dipeptide Phe-Phe self-assembled into diverse nanostructures. Reproduced from [34] with permission from the Creative Commons Attribution License.

functions [56]. The modified dipeptides containing an N-terminal ω-amino acid could self-assemble into nanotubes in the solid state and in aqueous solutions [57]. The morphological studies revealed the self-assembly of uniform and well-organized nanotubes with various dimensions. These modified dipeptide self-assembled nanostructures are significantly different from the solid-state or solution methods, which demonstrated that the self-assembly mechanisms in these two strategies are different [58]. Therefore, water molecules with hydrogen bonding capacities could have an important function in the self-assembly or even stabilization of the nanotubes.

Except for the dipeptides self-assembled nanostructures, there are also many other short linear peptides self-assembled nanostructures for biomedical applications including drug delivery [59, 60]. For example, KLVFF, a short peptide from amyloid-beta peptides self-assembly mechanism from Alzheimer's disease, could also self-assemble into nanofibrous structures and then hydrogel format in a concentrated phosphate buffered saline solution. The experimental results from physical and chemical characterizations have demonstrated that the linear short peptides can self-assemble into β-sheet structures and then form nanofibrillar hydrogel structures through electrostatic interactions [59]. Moreover, the short linear peptides DFNK and DFNKF both have been demonstrated to self-assemble into nanofibril structures based on the effects of pH values. These peptides have aromatic and charged side chains in the peptide sequences [60].

2.2. Cyclic Peptide. Cyclic peptides with alternating D type and L type amino acids that could self-assemble into nanotubes were determined theoretically as early as 1974 [61]. However, the first self-assembled nanotube using cyclo-(L-Gln-D-Ala-L-Glu-D-Ala)$_2$ cyclic peptides was achieved in 1993 based on that theory [62]. The cyclic peptide self-assembly is formed through aggregating cyclic peptides as basic building blocks to a flat conformation structure where the amino and carbonyl side chains are arranged perpendicular to the ring [63]. The cyclic peptide self-assembled nanotubes were self-assembled and stabilized by hydrogen bonding between amide groups shown in Figure 3 [64]. Due to the alternating D type and L type amino acids, the peptide side chains could be formulated on the outside area that can create a nanotube structure. There are many cyclic peptide sequences that can be used for the self-assembly, including alternating D type and L type α-amino acids, alternating α- and β-amino acids, β-amino acids, and δ-amino acids [62, 63, 65, 66].

In comparison to the other peptide self-assembled nanostructures, cyclic peptide self-assembled nanotubes have unique properties such as precise diameter controls, which could be tuned through the peptide sequences and lengths. The functions of the nanotubes could also be tuned by modifying the peptide side chains [63]. For instance, the internal diameter of the cyclic peptide could increase from 2 Å to 13 Å after increasing the peptide length from 4 to 12 amino acids [2, 66]. Moreover, the eight-residue cyclic peptides with the sequence of cyclo-(L-Gln-D-Ala-L-Glu-D-Ala)$_2$ can not only self-assemble into nanotube structures, but also self-assemble into nanoparticles with different methods and self-assembly parameters shown in Figure 4 [18].

For example, cyclic peptide self-assembled nanotubes have been prepared using eight-residue cyclic peptides containing Glu and Cys amino acids, which have been demonstrated for drug delivery applications [67]. The results have claimed that polyethylene glycol modified doxorubicin loaded nanotubes have high drug encapsulation ratio. More importantly, compared to free doxorubicin, the polyethylene

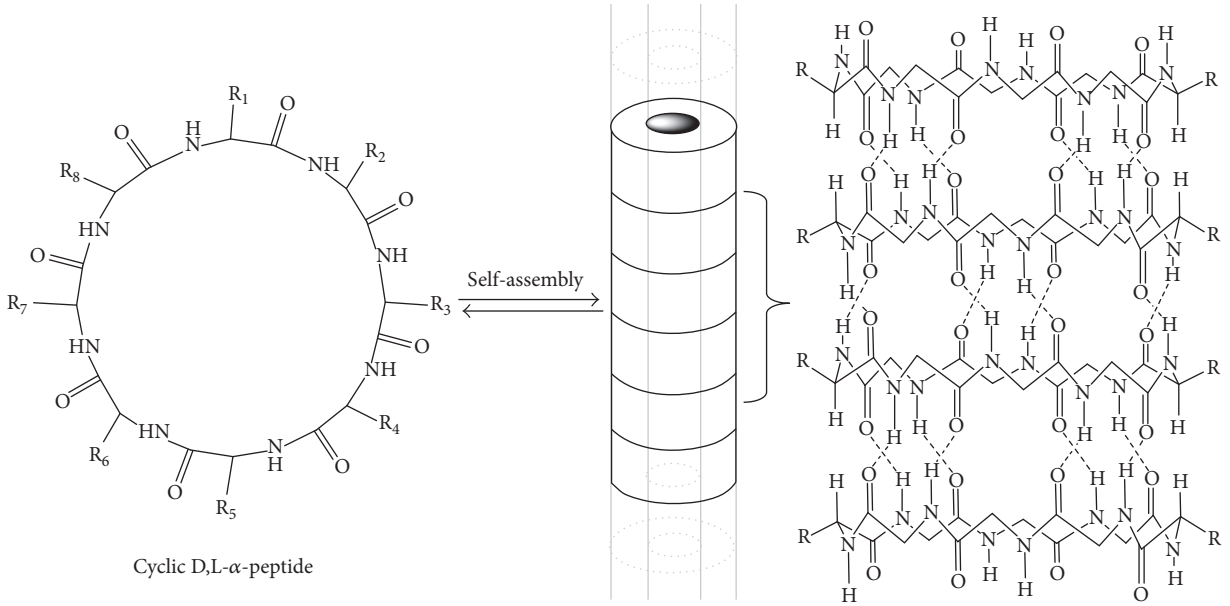

FIGURE 3: The schematic of the eight-residue cyclic D,L-α-peptide self-assembled nanotubes through hydrogen bonding. Reprinted with permission from Macmillan Publishers Ltd.: Nature [64].

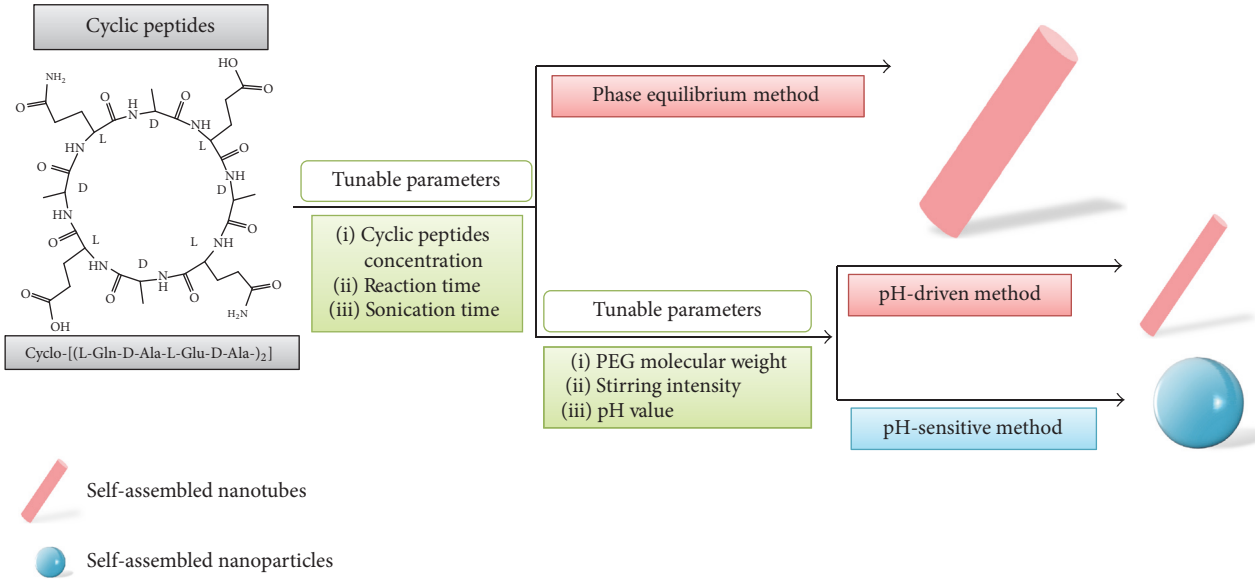

FIGURE 4: Schematic of the eight-residue cyclic peptides self-assembled nanotubes and nanoparticles. Reproduced from [18] with permission from the Royal Society of Chemistry.

glycol modified nanotubes with doxorubicin have been demonstrated to be with higher cytotoxicity and raised DOX uptake in human breast cancer MCF-7/ADR cells in vitro. Moreover, the polyethylene glycol modified nanotubes with doxorubicin have shown their potential in multidrug resistance tumor therapy [67].

2.3. Amphiphilic Peptide. Amphiphilic peptides have many different types such as linear peptides, ionic complementary peptides, peptide phospholipids, and long-chain alkylated peptides [68, 69]. Amphiphilic peptides are generally formed from hydrophilic peptide head groups and hydrophobic tails that could be used to form various secondary and tertiary conformations [70, 71]. These peptides could self-assemble into nanostructures with many different morphological structures including nanovesicles, nanotubules, and nanomicelles [69, 72]. The electrostatic and hydrophobic interactions are thought to be the main factors that drive the self-assembly for amphiphilic peptides [73].

Linear peptides with hydrophobic tails and hydrophilic heads have the ability to self-assemble into different nanostructures depending on their chemical properties and

physical properties. For the hydrophobic tail, A, G, L, and F amino acids are good candidates. On the other hand, the amino acids D, E, H, and R are always utilized in the hydrophilic domains [74]. For example, lipid-like peptides similar to surfactants, such as G_4DD, G_6DD, G_8DD, A_6D, A_6K, and KA_6 sequences, can self-assemble into various nanostructures once they reach the critical aggregation concentration [73, 75]. Because they are very similar to phospholipids, those peptides have the potential to stabilize membrane proteins.

The ionic complementary self-assembling peptides EAK16 were first discovered in 1993 with the formation of nanofibers [76]. These peptides have charged side chains in one side group and hydrophobic chains in another side group. The hydrophobic side chains could form a sheet structure inside the nanofibers. Meanwhile, the charged side chains could be laid on the outside of the nanofibers. Therefore, a stable structure could be formed from the repeated positively and negatively charged amino acids in the peptides sequences through ionic complementary forces [77]. Finally, they can self-assemble into typical β-sheet structures and then form a hydrogel structure which is composed of nanofibers. These hydrogels could be very stable under various ranges of conditions such as pH, temperature, and organic solvents because of the hydrogen bonding and ionic force [78].

Transparent hydrogels could be formed in seconds using amphiphilic peptides as soon as they react with physiological fluids [79]. This ionic complementary self-assembled peptide hydrogel is composed of more than 99% water. Therefore, there are plenty of spaces between the nanofibers inside the hydrogels. These types of peptide self-assembled nanostructures have been utilized to advance cell growth and differentiation in bone, cartilage, heart, and neural systems [80–85].

2.4. α-Helical Peptide. For decades, it has been well known that biological and physical properties can enhance the self-assembly of peptides into helical structures. Actuarially, there are only several major molecules that have been discovered with the purpose of self-assembling these helical structures into nanostructural biomaterials. The α-helical peptides have drawn researchers' attention because they can form nanostructures that are very common in the cytoskeleton and extracellular matrix in biological systems [86]. For example, these filamentous nanostructures could be formed from α-helical peptides with 25–50 amino acids [87]. The α-helical peptides with 2–5 helices can aggregate around each other to form nanofibers [88, 89]. These α-helical peptides can also self-assemble into nanofibers using around 30-amino-acid-long peptides through helical coiled-coils structures [90]. The hydrophobic residues could promote the helix oligomerization through hydrophobic collapse. Another nanofibrous structure could also be formed using the peptides with central Glu amino acid and Lys amino acid at the end of the sequence through ionic interactions [91].

Hydrogels could also be self-assembled from helical peptides with triblock motifs that have coiled-coil blocks [92]. Through the repeated hydrophobic and charged amino acids in the peptide sequence, coiled-coil structures could be self-assembled from α-helices [93]. Moreover, through tuning the length and structure of the basic coiled-coil units, the hydrogel properties also could be managed [94]. Therefore, these materials could be proposed to be a stimuli responsive hydrogel for drug delivery applications.

2.5. β-Sheet Peptide. The β-sheet is one of the most useful naturally occurring motifs that can be used for peptide self-assembly [95]. Tremendous peptides have been studied for self-assembling β-sheet secondary structures. The β-sheet consists of alternating hydrophilic and hydrophobic amino acids in the peptide sequence, which can provide amphiphilic property to the peptide that drives the self-assembly of β-sheets [96]. The β-sheet peptides also could be utilized to form many different nanostructures including nanotubes, monolayers in nanoscale order, and nanoribbons [97–101]. For example, β-sheet peptide QQRFEWEFEQQ can self-assemble into a pH responsive hydrogel using peptides' ionizable side chains from Glu and Arg amino acids. These peptides are soluble in neutral pH condition and transform to a hydrogel structure at low pH conditions [97]. The reason is that antiparallel β-sheet tapes were formed at lower pH values and then stacked together to form nanofibrils in hydrogels. The β-hairpin peptides were also found to self-assemble into various nanostructures at the water and air interfaces [102]. The self-assembly of β-hairpins in proteins is based on the arrangement of two β-sheets in antiparallel formats. A β-hairpin peptide with the sequence of VKVKVKVKVDPP-TKVKVKV was utilized to form responsive hydrogels. This material could be formed from the increase of the pH values. The underlying mechanism is that the hydrogels could be formed from the hairpin structure that was self-assembled from β-sheets formation after the increase of the pH values [103].

3. Peptide Self-Assembly Mechanisms

Electrostatic interaction, hydrophobic interaction, hydrogen bonding, and π-π stacking are the key contributors of peptide self-assembly [104]. Nonpolar amino acids, such as aromatic and aliphatic amino acids, are mainly responsible for hydrophobic aggregation through π-π stacking and hydrophobic interactions. Polar amino acids result in either electrostatic interactions or hydrogen bonding depending on whether they have uncharged or charged residues [105]. Besides individual amino acids, the peptide backbone itself also provides considerable stability through hydrogen bonds.

3.1. Electrostatic Interaction. Electrostatic interactions involve both attractive and repulsive forces between charged residues from amino acids in the peptide self-assembly, which also have strong effects on many other self-assembly processes. Positively charged peptides have the ability to aggregate with negatively charged peptides or even drugs by electrostatic interactions. After that, they could form a stable nanostructure that could be used for drug delivery applications [106]. For instance, a multifunctionalized peptide self-assembled nanostructure was designed and synthesized using

cRGD-BSA and KALA cell-penetrating peptides through electrostatic interaction. These nanostructures could be used for targeted and pH responsive anticancer drug delivery applications [107].

3.2. Hydrophobic Interaction. The hydrophobic interaction is one of the most important effects among various noncovalent interactions in the peptide self-assembly process. The self-assembly of amphiphilic peptides could be readily accomplished through microphase separation driven by thermodynamics because of the coexistence of polar and nonpolar regions inside the peptide sequences. In the aqueous reaction condition, the nonpolar segments of the basic units will collapse and cluster together to try to hide the hydrophobic area from water. Meanwhile, the polar areas attempt to enhance their contact with water [108, 109]. For instance, amphiphilic drugs that can be self-assembled into nanostructures were developed based on hydrophobic interactions. The amphiphilic drugs are composed of a tau protein derived peptide conjugated with a hydrophobic anticancer drug camptothecin. These materials could be self-assembled into fibril structures through hydrophobic interactions and intermolecular hydrogen bonding [110].

3.3. Hydrogen Bonding. Naturally occurring hydrogen bonding patterns such as those found in α-helices, β-sheets, and coiled coils are utilized for the design of various peptide sequences to self-assemble into nanostructures. Hydrogen bond is the electrostatic attraction between H atom and a highly electronegative atom nearby, such as N and O. Hydrogen bonding has a key role in the formation and stabilization of the peptide secondary structure and protein folding. Actually, among different noncovalent interactions, hydrogen bonding is probably the most important one in peptide self-assembly. The stabilization of multiple peptide backbone arrangements is based on hydrogen bonding interactions through the amide and carbonyls groups in the backbone. After that, they can self-assemble into β-sheet structures. These structures could be in parallel or antiparallel arrangements according to the direction of the peptide sequences. Peptide is typically designed to contain repeating amino acid residues for hydrophobic and hydrophilic regions. Therefore, the hydrophobic part will be buried within the self-assembled nanostructure while the hydrophilic region is exposed to the aqueous environment [111]. Unlike β-sheets, α-helices are formed by individual peptide chains where backbone amide components are intramolecularly hydrogen bonded. This arrangement leads to the presentation of side chains from amino acids on the surface of each helix and further facilitates the accessibility of them in the solvent.

3.4. π-π Stacking. The π-π stacking can promote the peptide self-assembly, especially for aromatic peptides. The interactions for π-π stacking can drive directional growth and they are robust in water due to their limited solubility of molecules containing aromatic groups [112]. The π-π stacking is also a more distinct driving force in pure organic solvents such as toluene and TFA. These solvents can make the π-π stacking more dominant than other self-assembly effects [40]. For the dipeptide FF self-assembly process, π-π stacking from the aromatic groups and hydrogen bonding stabilized the self-assembled FF nanostructures, which have been demonstrated for various applications including drug delivery [43, 113].

In summary, noncovalent interactions play very important roles in the peptide self-assembly processes. As these noncovalent interactions are easily affected by the external stimuli, these factors including pH values, temperature, and reaction solvent polarity can also trigger the self-assembly and manipulate the self-assembly process and even the final formed nanostructures. For example, pH values are very important for peptides with charged amino acids such as Glu, Asp, Lys, His, and Arg. The status of these peptides with negative or positive surface charges could be sensitively affected by the pH values and then self-assembled into different nanostructures [18]. Tunable management of the physical and biological properties of peptide self-assembled nanostructures is highly desired for their successful utilization in drug delivery applications. When designing peptide self-assembled nanostructures for drug delivery, noncovalent interactions, as well as peptide types and structures, should be taken into consideration and be rationally applied in the strategies.

4. Drug Delivery Applications of Peptide Self-Assembled Nanostructures

In the past decades, peptide self-assembled nanostructures with various sizes and shapes have been fabricated and utilized for many biomedical applications such as tissue regeneration, biosensors, bioimaging, and drug delivery. In this section, peptide self-assembled nanostructures for anticancer drug and gene drug delivery as well as targeted and stimuli responsive drug delivery are illustrated and discussed in detail. The most desired properties for self-assembled nanostructures are biocompatibility, biodegradability, and multifunctionality for drug delivery applications [17, 114]. Compared to other organic materials for drug delivery, peptide self-assembled nanostructures are more suitable due to their intrinsic physical and biological properties.

4.1. Anticancer Drug Delivery. Although tumors are one of the most deadly diseases worldwide, the proper therapy strategy is still far away from the real demand. Therefore, there is still a need for new materials or methods for cancer therapy. Nanomaterials as drug delivery carriers have many advantages including high efficiency for drug loading, a low ratio for drug loss, and high stability to avoid body clearance [115]. For example, nanostructures could be used for anticancer drug delivery because they have the ability to both enhance the therapeutic efficiency and decrease unwanted negative reactions. Among various nanostructures, peptide self-assembled nanostructures have attracted increasing attention for anticancer drug delivery and are believed to be a promising strategy for cancer treatment. The peptide has the ability to self-assemble into many different nanostructures such as nanoparticles, nanotubes, nanovesicles, and nanofibers that form hydrogels [116]. All of them could be used to deliver different types of anticancer drugs

for cancer therapy. For instance, the peptide with amphiphilic properties could self-assemble into nanovesicle structures, which have been demonstrated to deliver hydrophobic anticancer agents for cancer therapy. Meanwhile, the outside layer of these nanostructures could be tuned to achieve specific drug delivery purposes [117]. Peptide self-assembled hydrogel with injectable properties could also be used to directly come into contact with the tumor sites to enhance the efficacy and safety of tumor therapy [118]. Peptide self-assembled nanotubes also could be utilized for cancer therapy through conjugation with doxorubicin in high efficiency [113]. There are many different anticancer agents including doxorubicin, curcumin, fluorouracil, and paclitaxel that have been loaded in the peptide self-assembled nanostructures and investigated in preclinical or clinical trials for cancer therapy. Recently, there is much more progress in cancer therapy from peptide self-assembled nanostructures because of their excellent biodegradability and biocompatibility.

The peptide self-assembled nanofibers that form injectable hydrogels could be the most interesting materials for anticancer drug delivery applications, because, in this way, the chemotherapeutic drugs could directly come into contact with the targeted cancer tissues at higher local concentrations compared with traditional cancer therapy methods. These peptide hydrogels could be more safe and controllable due to their slow release rates. For instance, stimuli forming hydrogels self-assembled from KLD motifs can be used to tune the release of conventional cytotoxic anticancer drugs such as doxorubicin [118].

The nanofiber structures which self-assembled from the EAK peptides have been demonstrated to deliver anticancer drug ellipticine through encapsulation method. Two methods were used for the analysis of the self-assembly and drug delivery applications. The first one is the UV-based approach. In this method, the result revealed that the conjugation between the peptide and anticancer drug ellipticine was based on electrostatic interactions. Moreover, this method also could be used to detect the efficiency of drug loading in the peptide self-assembled nanostructures. The second approach is to use fluorescence technologies, which have the ability to monitor the conjugation process and efficiency. From the results, we could detect the concentrations of anticancer drug ellipticine in the whole self-assembly and delivery process through monitoring the fluorescence properties. The in vitro experiments also demonstrated that the encapsulated anticancer drug ellipticine in the self-assembled nanofibers in protonated stage is more efficient than in the crystalline stage for cancer therapy. These EAK peptide self-assembled nanostructures and the two encapsulation methods could also be used for some other anticancer agents in drug delivery for cancer therapy [119].

Dendrimer tetrapeptide GFLG self-assembled into compact nanoparticles with negatively charged surfaces after conjugation with PEG and anticancer drug doxorubicin. The drug loading and releasing experiments have demonstrated the 9.62 wt% drug loading efficiency as well as the enzyme responsive drug delivery applications. Fluorescent and cell studies revealed stable and effective cancer therapy compared with free doxorubicin anticancer drugs. Moreover, this study showed the decreased toxicities from doxorubicin anticancer drug as well as nondetectable side effects [120]. In addition to that, peptide self-assembled multifunctional nanostructures with dual-functional liposomes have also been developed for targeted drug delivery in cancer therapy. This system could be used for anticancer drug delivery through conjugation with cell-penetrating peptide and active targeting agents. In this study, R6H4 was screened for pH responsive anticancer drug delivery purposes. Hyaluronic acid was used to coat the R6H4 peptides due to their rapid degradation property. The in vitro and in vivo experiments have demonstrated that these nanocarriers could enhance the efficiency of tumor-targeted drug delivery in cancer therapy, as shown in Figure 5 [121].

Peptide-based hybrid nanostructures were also fabricated from polylactide (PLA) and VVVVVVKK (V6K2) peptides [75]. These nanostructures could conjugate with doxorubicin and paclitaxel for anticancer drug delivery in cancer therapy applications. The pure PLA nanoparticles have a diameter of around 130 nm, but the PLA-V6K2 self-assembled nanoparticles only have a diameter of around 100 nm. The encapsulation and anticancer drug releasing ratios for PLA-V6K2 nanoparticles are significantly higher and slower than the pure PLA nanoparticles. Moreover, the experiments have demonstrated that the PLA-V6K2 nanoparticles conjugated with anticancer drugs have higher toxicity to cancer cells and no toxicity to normal cells compared with free doxorubicin or paclitaxel and pure PLA nanoparticles conjugates. Therefore, this study demonstrated the higher efficacy of these PLA-V6K2 nanoparticles for anticancer drug delivery that could be potentially useful in cancer therapy [123].

4.2. Gene Drug Delivery. The great progress in biotechnology, as well as many other fields with better acknowledgment of the pathology mechanisms for various diseases from the gene levels, has promoted a big change in many different diseases' diagnosis and therapy. Researchers have used recombinant plasmid DNA as a gene drug for delivery to the specific target for gene therapy. In this way, the functional proteins from the related gene encoding could be applied to heal patients. The gene drug delivery needs cost-effective methods and noninvasive approaches for this specific gene disease therapy [124]. Although more and more attention has been paid to gene therapy, there is still huge enhancement needed for the study of nonviral gene drug delivery platforms currently. For example, the nanocarriers for gene drug delivery should be improved through different perspectives including toxicity, immunogenic response, and poor uptake into cells and the nucleus [125, 126]. Therefore, attention for the design and fabrication of nanostructures for gene drug delivery should be paid to the enhancement of cellular delivery, specific delivery, and improvement of loading efficacy. Cationic nanostructures have been intensively studied and utilized because they are easier to be delivered into cells and because of their high loading capacity for nucleic acids [127]. Most importantly, peptide self-assembled nanostructures present a very promising and efficient method for gene drug delivery due to their intrinsic properties and precisely controllable fabrication approaches. Peptide self-assembled nanotubes also could be used for gene drug delivery through the

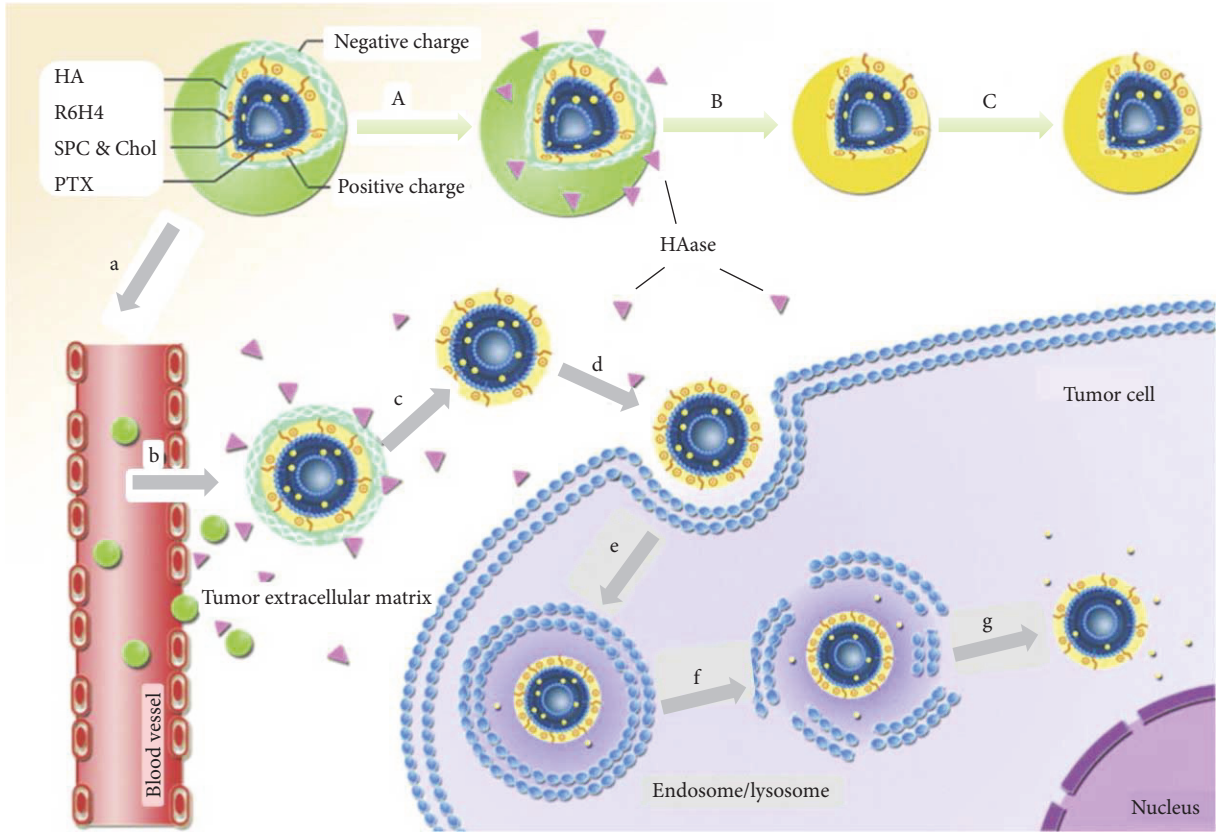

Figure 5: Schematic design of the multifunctional nanostructures for tumor-targeted drug delivery. Reprinted from [121] with permission from Elsevier.

transforming of nanotube structures into nanovesicles in the endocytosis process [128]. Therefore, many conjugations of gene drugs and peptide self-assembled nanostructures have been developed recently for the gene drug delivery systems [129].

The surfactant peptide could be self-assembled into nanotubes or nanovesicles with a diameter of around 50 nm. This type of surfactant peptide was designed based on the cationic lipid systems for better gene drug delivery applications. The peptides monomers are around 2 nm in length. The head of the peptide is cationic and hydrophilic with one or two Lys and His amino acids. After that, there are six amino acids including Ala, Val, or Leu to form the peptide tail with hydrophobic properties. When the pH values are higher than the pI, these nanostructures could be further self-assembled into nanosheet structures. Because of the unique self-assembly and charge properties, these cationic peptides self-assembled nanostructures could be very useful to conjugate negatively charged DNA and RNA for efficient gene drug delivery applications [75].

A peptide including four segments conjugated with the lipopeptide transfection gene drugs has been developed recently for gene drug delivery applications in gene therapy. The peptide is composed of cysteine, lysine, histidine residues, and the alkyl chains. These nanostructures were self-assembled for the delivery of gene drugs into cells through histidine residues. The delivery of gene drugs into the nucleus was promoted by the lysine residues with charges at neutral pH values. Therefore, after the design, synthesis, and evaluation, these peptide self-assembled nanostructures have been demonstrated to be with high transfection efficiency for gene therapy through gene drug delivery [130].

A targeting peptide GE11 with branched structures has been developed and self-assembled into nanostructures with other components for gene drug delivery as shown in Figure 6; the peptide-based nanostructures were composed of the GE11 targeting peptide, branched polyethyleneimine, S-S bond, and polyethylene glycol [122]. The experimental results have demonstrated that both GE11 and branched GE11 self-assembled nanostructures have efficient capability for gene condensing and transfection. Moreover, they also have low toxicity and increased capability for targeting. Most importantly, compared to the GE11 self-assembled nanostructures, the branched one has a higher capability for targeting cancer cells with overexpressed EGFR. Therefore, this study has demonstrated that the peptide self-assembled nanostructures could be very useful for gene drug delivery in gene therapy.

One of the most important properties of peptide self-assembled nanostructures for gene drug delivery is the conjugation between these nanostructures with DNA. Moreover, because of the easier modification and tunability of the

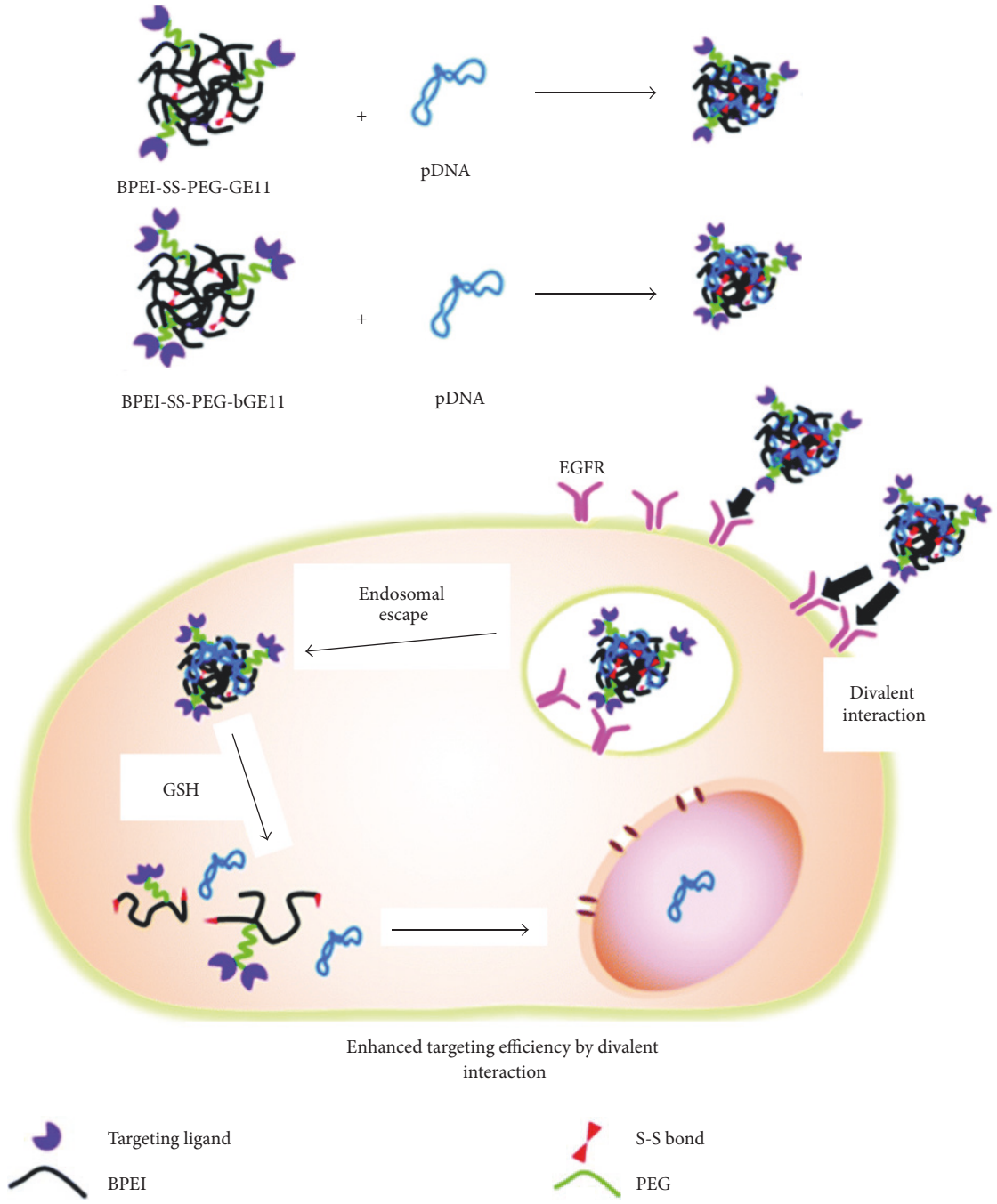

Figure 6: Schematic of gene drug delivery by using GE11 peptide-based self-assembled nanostructures. Reproduced from [122] with permission from the Royal Society of Chemistry.

peptide building blocks, these peptide self-assembled nanostructures could also increase the DNA uptake through cell membrane and nucleus. They also have the ability to control the gene drug release and enhance gene expression [131]. Therefore, researchers could focus on developing vectors with improved efficiency, safety, and specificity. Although there are several studies using peptide self-assembled nanostructures for gene drug delivery, it is still far away from the real demand.

4.3. Targeted Drug Delivery. For drug delivery applications, specific targeting with desired sites is very important for the nanocarriers to deliver or transport the drugs efficiently [132]. For this purpose, peptides self-assembled nanostructures have many advantages such as easier modification properties and tunable design of the recognition motifs. For example, cell-penetrating peptides are cationic peptides with less than 30 amino acids, which could be used to

promote the penetration of the cell membrane to make the drug or gene delivery more efficient [133]. Most importantly, the self-assembly mechanism is also very important for the enhanced membrane transport using cell-penetrating peptides. Besides that, there are also many other proteins or aptamers that could be used to enhance cell penetrating or specific targeting especially for cancer cells or disease sites. For example, dipeptide WF self-assembled nanoparticles have been developed for targeted drug delivery for cancer therapy [15]. These peptide self-assembled nanoparticles have visible fluorescent properties compared to amino acids' intrinsic UV range fluorescent properties. The self-assembly and fluorescence generation mechanisms are inspired from the green fluorescent protein (GFP) and yellow fluorescent protein (YFP). Through that, this dipeptide including tryptophan and phenylalanine could self-assemble into blue light fluorescent nanoparticles through π-π stacking and zinc coordination interactions. The experimental results have demonstrated that these nanostructures are biocompatible and photostable, except the blue color fluorescent properties with a narrow emission wavelength. Most importantly, these dipeptides self-assembled nanoparticles could conjugate with MUC1 aptamer and anticancer drug doxorubicin to target specific cancer cells for better delivery and cancer therapy applications [15]. These studies revealed the potential and advantages of using peptide self-assembled nanostructures for targeted drug delivery applications.

The peptide self-assembled nanostructures could be in many different formats that have the advantages of specific targeting and could conjugate with many drugs such as anticancer and gene drugs for the delivery system [134, 135]. For example, one functional nanostructure could be self-assembled with many different targeting peptides and drugs with multiple purposes. The supramolecular nanoparticles self-assembled with specific targeting motifs including cancer cells and nucleolus have been developed for targeted drug delivery in tumor therapy and gene therapy [136, 137]. The functional peptides with lots of arginines could be used to bind with RNA sites for condensed siRNA for the targeted gene drug delivery applications in this system. The tumor cell targeting peptides could also be introduced into this system for the targeted anticancer drug delivery for cancer therapy. The electrostatic interactions play the main role in the self-assembly processes. The experimental results have demonstrated that these peptide self-assembled nanostructures could specifically target the hepatocellular carcinoma cells efficiently.

A capsid-like nanostructure self-assembled from dendrimer peptides and functionalized peptides has been developed for targeted drug delivery in cancer therapy [138]. These dendritic nanostructures are designed and self-assembled using a supramolecular method to mimic the capsid-like structures and similar components. The functionalized peptides were selected for specific targeting of cancer cells. These designs have many advantages for targeted drug delivery for tumor therapy. For example, the capsid-like nanostructure could be used to promote drug penetration through many different barriers. The peptide self-assembled nanostructures with well-ordered structures also could enhance the drug accumulation in targeted disease areas. Most importantly, the functionalized nanostructures could be used for specific delivery to the targeted tumor sites. The experimental results have confirmed the advantages and demonstrated that these nanostructures loaded with doxorubicin have the ability to treat tumors in BALB/c mice with low toxicity efficiently [138].

Functional peptides have also been used for targeted drug delivery for biomaterials such as liposomes to improve specific targeting and cell penetrating [139]. For example, the PR_b peptide, as well as polyethylene glycol, could be used to self-assemble into nanostructures with liposomes in a good manner. The PR_b peptide in this system could be used to specifically bind with the overexpressed integrin $\alpha_5\beta_1$ in colon cancer cells. The polyethylene glycol could be utilized as a steric barrier to protect the nanostructures. Therefore, these coated peptide self-assembled nanostructures could stay longer in the circulating blood system. The experimental results clearly demonstrated the capability of these functional nanostructures for targeted delivery of anticancer drugs into colon cancer cells. Therefore, they can decrease the tumor metastasis and reduce the tumor growth with limited side effects.

4.4. Stimuli Responsive Drug Delivery. Peptides have the ability to self-assemble into well-defined nanostructures which have many different formats including nanofibers or hydrogels for tissue regeneration, drug delivery, and so on [118, 140]. Peptide self-assembled hydrogels are biodegradable and biocompatible and are easier to be modified with specific materials such as small molecules or peptide ligands [92]. Therefore, biocompatibility and biodegradability could be realized through the peptide-based self-assembly due to their incorporation of biological advantages in the specific targeting and sensitive reaction sites [103]. Importantly, these peptide self-assembled nanostructures should have the capability for controlled release of the loaded drugs or other materials when they are triggered by the environmental factors. The releasing time, ratio, or many other strategies should be controlled under the requirements of the disease status. Therefore, the peptide self-assembled nanostructures with stimuli responsive properties and well-controlled releasing functions could be used to increase the drug delivery efficiency and then for therapeutic purposes [141].

Peptide self-assembled nanostructures especially the hydrogel formats are very important classes of hydrogels, which have attracted much attention recently as a drug delivery platform because of their high drug loading efficiency, controlled drug release, and responsive drug release under different stimulations such as pH value and temperature [141]. For example, a hydrogelator system has been developed based on peptides with anticancer drug curcumin. The basic building blocks are curcumin-FFE-ss-ERGD. The peptides FFE and disulfide bond have been proven to have the ability to form supramolecular hydrogelator structures. The ERGD peptides could be used for the specific targeting of cancer cells. In addition, these peptide self-assembled nanostructures could also be responsive to pH change after endocytosis and then disassembly into single molecules. The in vitro and

in vivo experimental results have demonstrated that these systems could enhance the cellular uptake and controlled and responsive drug releasing. Therefore, they have the potential to inhibit cancer cells and tumor growth through stimuli responsive drug delivery for cancer therapy.

The peptide self-assembled fiber-like nanostructures have been developed using cleavable amphiphilic peptide for stimuli responsive anticancer drug delivery application in tumor therapy [142]. These nanostructures could be formed by spherical nanoparticles after the loading of hydrophobic chemotherapeutic drugs. These nanoparticles have been demonstrated to be responsive to fibroblast activation protein α, which could be overexpressed on the surface of cancer-related fibroblasts cells. These nanoparticles could be disassembled specifically at the tumor sites with efficient and rapid release of the conjugated anticancer drugs. Therefore, this system has the ability to promote the local accumulation of drugs through the disruption of stromal barriers.

There are also many other peptides or proteins including IgG, bovine serum albumin, and lysozymes that can be used to conjugate with Ac-$(RADA)_4$-$CONH_2$ peptide hydrogel for stimuli responsive drug delivery applications [143]. The mixing of the therapeutic-based proteins and peptide solution could be utilized for drug release with the controlled manner in specific tissues. Moreover, peptide self-assembled nanostructures that are responsive to temperature or magnetic field also have been developed and validated for responsive drug delivery applications [144]. For example, the peptide self-assembled nanostructures coated with chitosan/ELR shell could be responsive to temperature for controlled drug release. The chitosan/ELR has the temperature responsive function in this system. Depsipeptide self-assembled nanostructures were also designed to overcome the resistance to degradation by protease for peptide self-assembled nanofibers [145]. These nanostructures are self-assembled using the peptide sequence with ester bonds. Therefore, the depsipeptides self-assembled nanostructures can degrade from days to weeks by the ester hydrolysis processes for the enzyme responsive drug delivery applications.

5. Conclusions and Perspectives

Peptide self-assembled nanostructures could construct well-defined structures through the noncovalent forces including electrostatic interaction, hydrophobic reaction, hydrogen bonding, and π-π stacking. The morphology and function of the peptide self-assembled nanostructures can be manipulated from the molecular level by tuning the types and structures of peptides, or external triggers such as temperature, pH value, and electric field. Recent studies have shown that these peptide self-assembled nanostructures have been utilized for many different biomedical applications. The examples presented in this paper highlight the potential role of peptide self-assembled nanostructures for drug delivery applications. One peptide self-assembled nanostructure could include multiple functions such as cell penetration, specific targeting, release responsive mechanism, and endosomal escape motifs. However, people are still facing many challenges such as predicting precise molecular or higher structures, functional properties, and biosafety from the peptide self-assembly. Another major challenge is the high yield of the peptide nanomanufacturing. This is also very important for the clinical applications. In conclusion, with multidisciplinary efforts, peptide self-assembled nanostructures for drug delivery applications have much potential and are very promising to treat human diseases.

Conflicts of Interest

The authors declare that they have no competing interests.

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