Gang Wei *Editor*

Peptide Nano-Chemistry and Nanotechnology

From Molecular Design, Self-Assembly, Biomimetic Synthesis to Applications

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About This Book

Peptide with desired structure and functions has been widely used for materials science and nanotechnology due to their tailored sequence, high activity, self-assembly ability, biomimetic activity, and others. To present the progress of peptides in nano-chemistry and nanotechnology, this bok presents 14 chapters on the aspects of (i) synthesis and properties of peptides, (ii) functionalization and hybridization of peptides, and (iii) applications of peptide-based nanomaterials. This book demonstrates firstly the self-assembly of designed peptides to 1D, 2D, and 3D nanostructures. Secondly, this book introduces the hybridization of peptides with polymers, nanoparticles, carbon materials, and 2D materials through specific binding and biomimetic synthesis to create bioactive nanomaterials. Finally, the applications of peptide-based nanomaterials in materials science, nanotechnology, and biomedicine are demonstrated. This book will be helpful for readers to understand the chemical, physical, and biological properties of peptides, and further inspire the design and synthesis of functional peptide nanomaterials for advanced applications.

Contents

Chapter 1
Design and Self-Assembly of Peptide Amphiphiles

Xin Luan and Gang Wei

Abstract Peptide amphiphile (PA) is a small molecule containing both hydrophilic and hydrophobic motifs in the peptide sequence. As it is designed from natural amino acids, it exhibits good biocompatibility, high bioactivity, and high biodegradability. Therefore, PA can be used as a flexible building block for the molecular design and utilization in various ways and has been widely used in various scientific and technical fields. In addition, PA shows the ability to self-assemble into various amyloid aggregates and can self-assemble into a series of functional nanostructures, such as nanofibers, nanotubes, spherical micelles, vesicles, nanosheets, and hydrogels. In this chapter, we focus on the design, synthesis, and self-assembly mechanisms of PAs. The effects of environmental adjusting, such as the interactions, pH, ionic strength, and temperature, on the self-assembly of PAs and the formation of supramolecular nanostructures are presented and discussed. This chapter will provide valuable information and inspirations for the rational design and synthesis of PA-based functional nanomaterials for biomedical and nanotechnological applications.

Keywords Peptide amphiphiles · Self-assembly · Nanomaterials · Biomedicine · Nanotechnology

1.1 Introduction

The self-assembly of biomolecules is a spontaneous behavior [1], in which biomolecules undergo a bottom-up way in various noncovalent (such as hydrogen bonds, electrostatic interactions, hydrophobic interactions, aromatic interactions, and van der Waals forces) and covalent interactions to form ordered nanostructures [2, 3]. Although the energy of the noncovalent driving forces in the self-assembly process is much lower than that of covalent bonds, it can still drive biomolecules to self-assemble into robust nanostructures [4]. Meanwhile, the formation of molecular

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aggregates that driven by noncovalent interactions was influenced by external conditions, such as the pH, temperature, and ionic strength [5]. When triggered by external or internal factors, the structure of molecular aggregates may collapse or transform [6].

Peptides are short oligomers of natural amino acids that linked by amide bonds [7]. Peptide-based biomolecules have attracted much attention due to their high biocompatibility, biodegradability, adjustable functionality, and design flexibility [8]. Previously, cyclic peptides, amphiphilic peptides, and ion-complementary peptides have been used as bioactive building blocks to construct functional nanostructures with different shapes via peptide self-assembly [9, 10]. Peptide amphiphiles (PAs) are small molecules containing both hydrophilic and hydrophobic moieties that coupled to a peptide bone sequence [11]. Among peptides for constructing functional nanostructures, PAs are becoming important due to their high biological activity and structural advantages [12]. The structural diversity of PAs determines the modes of their self-assembly processes and leads to the bottom-up self-assembly into ordered nanostructures, such as micelles, microemulsions, vesicles, liquid crystals, fibers, nanosheets, and hydrogels, showing potential applications in drug delivery, wound healing, tissue engineering, material science, enzymatic protection, and many others [13−15].

Although PAs showed great potential in the development of materials science and nanotechnology, the aggregation behavior of PAs was significantly affected by the structure of PA molecule [16]. In addition, the self-assembly pathways affected the shape, internal structure, and size of PA-based nanostructures, thereby affecting their biological activity [17]. Therefore, the exploration of the self-assembly mechanisms of PAs and the rational design of PAs with good effectiveness and stability are of great significance for the synthesis of functional peptide nanomaterials [18].

In this chapter, we discuss the knowledges of PAs and bring together recent progress on the self-assembly mechanisms and the design strategies of PAs. In addition, the effects of environmental factors such as the molecular interactions, pH, ionic strength, and temperature on the formation of PA nanostructures are introduced and discussed.

1.2 Classification of PAs

PAs can be divided into two categories, including (i) amphiphilic peptides and (ii) lipidized PAs. In this section, we focus on the structure and self-assembly behavior of two different types of PAs.

1.2.1 Amphiphilic Peptides

Amphiphilic peptides can be divided into two distinct sub-classes, including those containing alternating hydrophilic or hydrophobic amino acid residues, and those consisting of long stretches of hydrophobic amino acids that linked to hydrophilic sequences. The properties and aggregation behavior of these modified amphiphilic peptides show great difference.

Liang and co-workers designed and prepared a pH-responsive amphiphilic peptide (Fig. 1.1a) with the sequence of VVVVVVKKGRGDS [19], in which the hydrophilic head is the KKGRGDS sequence, and the hydrophobic tail composes of the VVVVVV sequence. The V (valine) residue in the hydrophobic tail contained a hydrophobic side chain, which can provide the hydrophobic forces. Therefore, the designed PA was driven by the hydrogen bonds and hydrophobic forces to self-assemble into spherical micelles in neutral or alkaline media and then transformed into nanofibers as the PA concentration increased. Subsequently, the antitumor drug, doxorubicin (DOX), was successfully loaded into the hydrophobic core of the self-assembled PA micelles. The lysine (K) residues in the hydrophilic head provided pH-responsiveness, and their ionization in the acidic tumor microenvironment (TME) provided electrostatic repulsion. Therefore, the self-assembled PA nanostructures were destroyed under this force, allowing the dissolution of PA micelles to achieve controlled release of DOX. In another case, Cheng et al. synthesized peptide nanoparticles for dual-targeted cancer therapy by tailoring the sequences of both hydrophilic and hydrophobic domains in a PA [20]. The hydrophilic domain composes of ^{D}PPA-1 (NYSJPTDRQYHF, all $_{D}$-type amino acids), and the hydrophobic domain consists of one lysine, two leucines, and two glycines as linkers to couple functional 3-diethylaminopropyl isothiocyanate (DEAP) molecules and matrix metalloproteinase-2 (MMP-2). The resulting PA and indoleamine 2,3-dioxygenase (NLG919) co-assembled into micellar nanoparticles at pH 7.4. At lower pH, the formed PA nanoparticles collapsed, and NLG919 and ^{D}PPA-1 were precisely released and targeted to tumor cells, inhibiting the growth of melanoma effectively.

Kim et al. used PA to construct a supramolecular nanoplatform for cancer theranostics [21] (Fig. 1.1b). In their study, hydrophobic peptide blocks with a tendency to form β-sheets were first selected, which were then driven to self-assemble into protonanofibers. The formed nanofibers were successfully loaded with anticancer drug, DOX. Then the targeted octreotide-labeled PA molecule was selected, and the paramagnetic metallic ion (Gd^{3+}) chelating ligand, 1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10 -tetraacetic acid (DOTA), was connected for cancer imaging. The co-assembly of PAs with biomedical functions and drug-carrying fibrils realized the transformation from proto-fibrils to helical fibrils, forming peptide nanofibers (PNFs) that could be targeted to human breast cancer cells (MCF-7) for magnetic resonance (MR) imaging.

Chen et al. designed a short PA molecule with high selectivity and antibacterial properties (Fig. 1.1c) [22]. The general chemical structure of the designed PA was

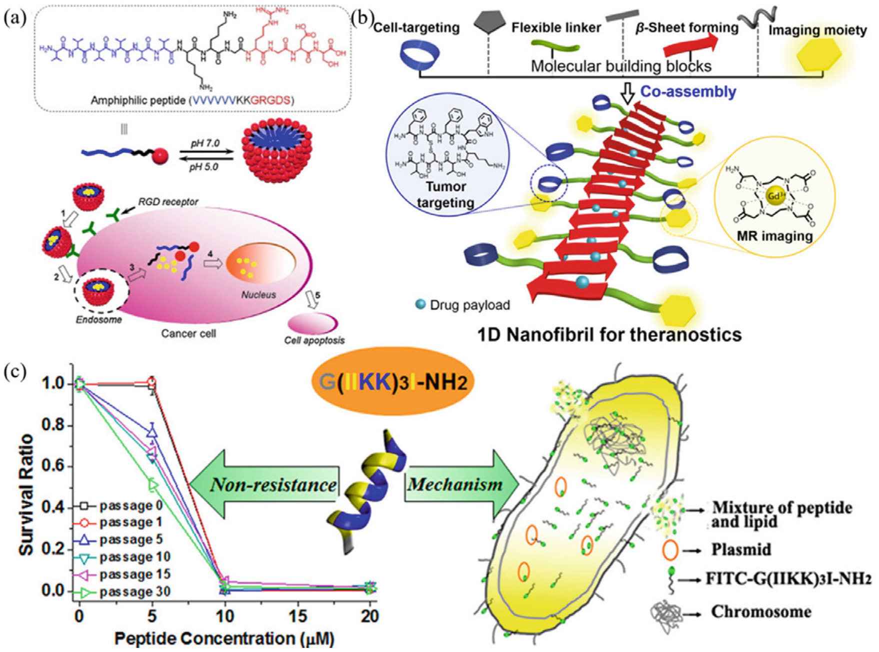

Fig. 1.1 Design and self-assembly of PAs: **a** pH-responsive self-assembly of the VVVVVVKKGRGDS PA. Reproduced with the permission from Ref. [19]. Copyright 2014, Elsevier. **b** 1D supramolecular nanoplatform fabricated by co-assembly of PA cancer therapy. Reproduced with the permission from Ref. [21]. Copyright 2016, American Chemical Society. **c** Antibacterial mechanism of G(IIKK)$_3$I-NH$_2$ PA. Reproduced with the permission from Ref. [22]. Copyright 2014, American Chemical Society

G(IIKK)$_n$I-NH$_2$ ($n = 2 - 4$). By regulating the number of the motif of IIKK, the designed PA revealed the highest cell selectivity and antibacterial toxicity. The short PA was positively charged under physiological conditions and could interact with the negatively charged cell membranes. Therefore, this PA transited from a random coil to an α-helical conformation, killing bacteria by selectively disrupting cell membranes with low toxicity to normal cells. The isoleucine in the peptide sequence provided the driving force for the formation of α-helical conformation, and the N-terminal-linked glycine and C-terminal-linked NH$_2$ improved the stability of the α-helical structure and the resistance to peptidases. The above factors all improved the selectivity of this short peptide with simple structure to the cell membranes of bacteria.

The preparation of functional PA co-assemblies for theragnostic purposes can be achieved by adding peptide building blocks with β-sheet propensity. The nanoscale morphology of PA aggregates in solution can determine the microstructure and properties of hierarchical self-assembled PA membranes. In a typical study, Zha et al. used a cytotoxic peptide to fabricate supramolecular membranes that could be used for cancer therapy [23]. A cytotoxic PA sequence of KLAKLAKKLAKLAK (KLAK PA) was selected, which specifically destroyed the cell membrane of cancer cells at a low concentration and leaded to the death of cells. The KLAK PA contains two types of α-helical sequences that can self-assemble into small spherical aggregates in solution. It was found that the diameter of the created spherical aggregates was adjustable by changing the PA concentration. In addition, the change of PA nanostructures from cylindrical to spherical aggregates was further discussed. Hydrophobic hyaluronic acid (HA) could be combined with cancer cells to accelerate the degradation of PA nanomaterials, and therefore, HA was co-assembled with the cytotoxic PA to form functional PA-HA membrane for drug delivery and cancer therapy.

1.2.2 Lipid PAs

In addition to PAs consisting of only natural amino acids, peptides bound to other components were also investigated. One of the most studied examples is that of PAs using an alkyl group as a hydrophobic tail. In the work of Xiao et al., a mesoporous silica nanoparticle (MSNPs) coated with a self-assembling PA was designed [24]. The hydrophilic amino acid sequence DSDDSDSDSRGDS was coupled with a hydrophobic alkyl side chain to form the lipid PA, C_{18}-DSDSDSDSRGDS. The alkyl chain stearic acid (C_{18}) was linked to the surface of MSNPs through disulfide bonds, as shown in Fig. 1.2a. The side chains formed a dense and compact network structure on the surface of the MSNPs under hydrophobic interaction, which firmly sealed the loaded DOX in the core of the MSNPs. In the presence of dithiothreitol (DTT) or glutathione (GSH), the disulfide bond was broken, and the drug was released successfully to the tumor sites. This study provided a new idea for the design and synthesis of self-assembled PAs as smart drug nano-platforms for cancer therapy.

Similarly, Ruan et al. mixed cell suspensions of bone marrow mesenchymal stem cells (BMSCs) with a PA containing IKVAV and fabricated peptide hydrogels with 3D nanofibrous structures via the peptide self-assembly [25]. The hydrophobic tail of the PA ($C_{16}H_{31}O$-$A_4G_3D_2$IKVAV) is a long alkyl chain composed of 16 carbon atoms, which provides hydrophobic interaction to drive molecular self-assembly. Four alanines were combined with three consecutive glycines to form A_4G_3, and the alkyl group acted synergistically, creating increasingly more hydrophobic residues away from the epitope. Aspartic acid carried negative charge at $pH < 8.5$ and electrostatically interacted with cations in solution. Driven by multiple forces, the designed PA self-assembled into PA hydrogels. The active sites of the IKVAV on the surface of the formed PNFs promoted the cell adhesion and axon outgrowth, thereby promoting successful differentiation of BMSCs into neural cells.

To deliver sufficient drugs into tumor cells, Du and co-workers designed a PA nanoparticle targeting the epidermal growth factor receptor (EGFR) [26]. The hydrophilic head of the PA composed of the EGFR targeting peptide (GE11) and the amino acid sequence of YHWYGYTPQNVI, and an additional Gly and two Glu-containing carboxyl groups were added to the hydrophilic sequence to increase the hydrophilicity of PA, as shown in Fig. 1.2b. C_{18} was attached to the hydrophilic sequence as a hydrophobic tail, which driven by the hydrophobic interaction to

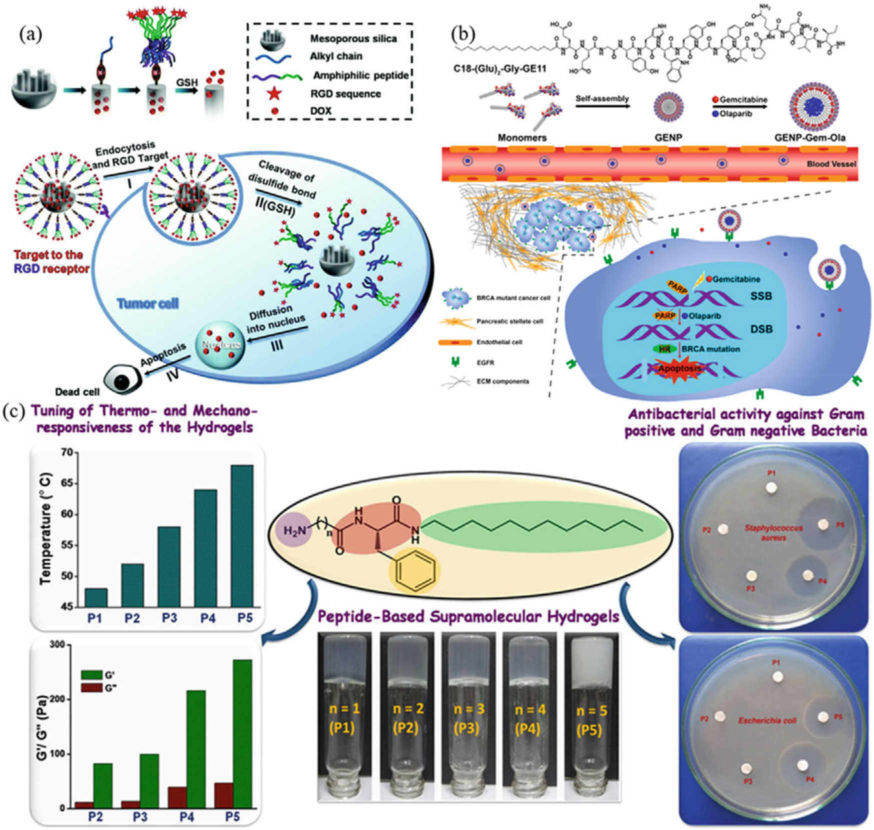

Fig. 1.2 Design and self-assembly of lipid PAs: **a** Structural schematic of RRMSN/DOX and redox-responsive cancer-targeted drug delivery. Reproduced with the permission from Ref. [24]. Copyright 2015, Royal Society of Chemistry. **b** Mechanism of EGFR-targeted self-assembly of PA nanoparticles for cancer therapy. Reproduced with the permission from Ref. [26]. Copyright 2018, American Chemical Society. **c** Molecular structures and self-assembly of amphiphilic peptides to hydrogels. Reproduced with the permission from Ref. [28]. Copyright 2017, American Chemical Society

form peptide nanoparticles. The synthesized PA nanoparticles could co-deliver two antitumor drugs, gemcitabine (Gem) and olaparib (Ola), to achieve high antitumor efficacy with precise targeting the overexpressed EGFR onto pancreatic cancer cells.

Furthermore, PAs with longer alkyl chains were more thermally stable than PAs with shorter alkyl chains [27]. Nandi et al. achieved the regulation of peptide self-assembly and the gel behavior by adjusting the length of the alkyl chain of amino acid residues at the terminal of the PA sequence [28]. In their work, they developed a series of lipid PAs with general chemical formula of [$H_2N–(CH_2)_nCONH–Phe–CONHC_{12}$ ($n = 1 - 5$, C_{12} = dodecylamine)], as shown in Fig. 1.2c. Among them, the C-terminal of the PAs was covalently linked to a long fatty acyl chain, and the N-terminal glycine/ω-amino acid residue was linked to a free amino group. The phenylalanine residues in the side chains provided the $\pi - \pi$ and hydrophobic interactions to drive the PA self-assembly into a thermo-responsive hydrogel with nanofibrous network structure. By changing the number of "*n*" in the general formula of PAs, the thermal stability, recovery time, and regulation of the affinity of the hydrogel to bacterial membrane were realized. When the alkyl chain at the end of the amino acid residue was longer, the self-assembled PA hydrogel exhibited clear antibacterial activity against *S. aureus*, *B. subtilis*, and *E. coli*.

Moyer and colleagues investigated the effect of pH and the sequence of PA on the self-assembled structures and corresponding drug loading efficiency [29]. First, a PA molecule consisting of an oligohistidine (H_6), an aliphatic hydrophobic sequence, and a solubilizing oligo(ethylene glycol) (OEG) group was designed. Tuning the nanostructure was achieved by attaching aliphatic hydrophobic tails to different peptide sequences. In one case, the aliphatic tail palmitic acid was attached to the N-terminus of the PA sequence, the OEG group was attached to the C-terminus, and the amphiphilic molecules of this sequence self-assembled into PNFs at pH 7.5. In another case, the C-terminus of the amino acid was connected to the aliphatic tail lauric acid, the N-terminus was connected to the OEG sequence, and the PA molecules self-assembled into spherical micelles at pH 7.5. In addition, the reversible self-assembly was achieved through adjusting the pH of system. Both self-assembled PA nanostructures were selectively dis-assembled under the influence of the histidine protonation at pH 6.0 to 6.5. Finally, compared with spherical micelles, PNFs exhibited superior antitumor drug encapsulation ability and tumor accumulation. This study demonstrated that the biomedical efficiency of peptide-based nanomaterials can be optimized by regulating the structure and sequence of peptide molecules.

1.3 Strategies for Regulating the Amphiphilicity

The number of amino acids can change the length of amphiphilic peptides, which directly affects the balance between hydrophilic and hydrophobic domains. Ashwanikumar and colleagues investigated the effect of the number of added amino acids on the self-assembled morphology of PA [30]. A single phenylalanine was added consecutively at the N-terminus of the PA (RADARADA). Increasing the number of phenylalanine changed the length of the peptide chain, increased the hydrophobicity, and broken the balance between the hydrophilic and the hydrophobic domains, as shown in Fig. 1.3a. The secondary structure of the cell-penetrating self-assembling peptide nanomaterials (CSPNs) transformed from random coils to twisted α-helices and β-sheets, eventually forming a stable α-helix. Driven by the $\pi - \pi$ interactions, PA molecules containing two, three, or four phenylalanines self-assembled into "nano-drill-like structures", which could effectively encapsulate hydrophobic molecules with a better internalization effect. Based on this study, it is concluded that functional PA nanomaterials with different structures can be designed by adjusting the number of amino acids.

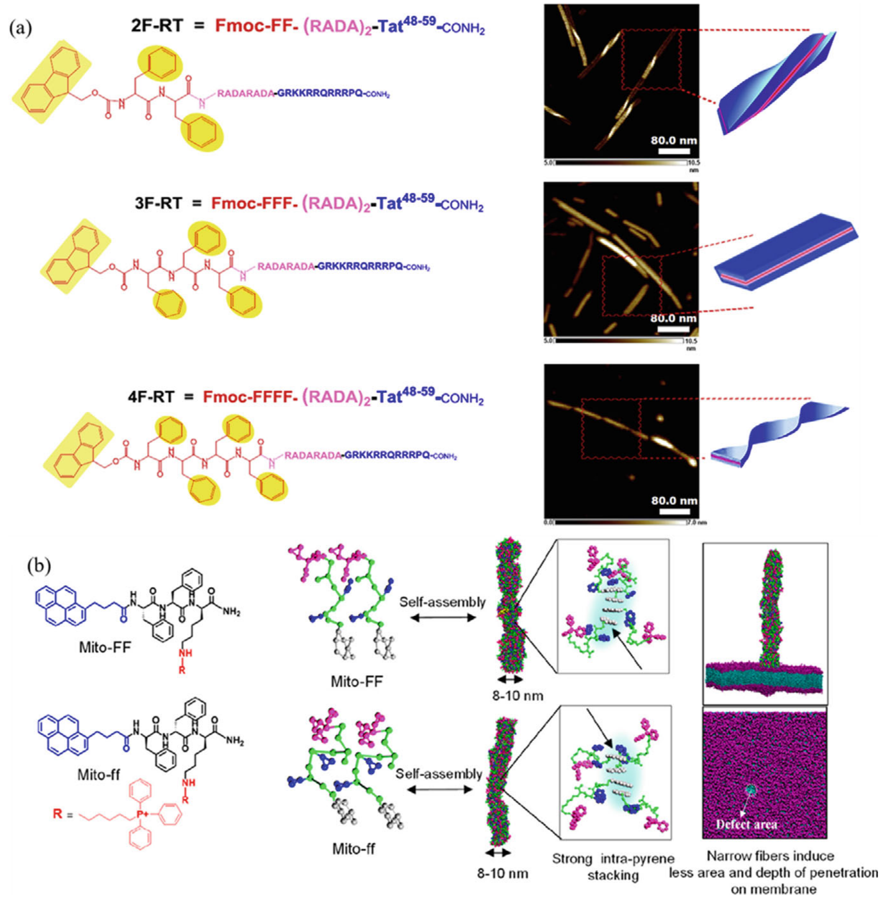

Fig. 1.3 **a** Structure and schematic diagram of CSPNs. Reproduced with the permission from Ref. [30]. Copyright 2018, Elsevier. **b** Chemical structures and self-assembled structure of two mitochondrial penetrating peptides. Reproduced with the permission from Ref. [35]. Copyright 2019, American Chemical Society

In a similar study, Lin et al. designed self-assembled monolayer Janus nanosheets from amphiphilic peptides [31]. The amphiphilic peptide was designed from the hexaphenylalanine, a hydrophobic tail, and glutamic acid and could self-assemble into Janus nanosheets with a monolayer thickness of about 5 nm. The driving forces for the formation of two-dimensional (2D) nanosheets were mainly from the configuration of aromatic amino acids and hydrocarbon chains. Among them, the alkyl chains promoted hydrophobic interactions and enhanced peptide association in the x- and y-axis directions. Meanwhile, phenylalanine promoted the β-sheet stacking in the y-axis direction. When the number of phenylalanines in the peptide chain was reduced, the self-assembled PA nanostructure also changed from 2D nanosheets to distorted 1D fibrils.

In addition, changing the relative positions of amino acids can also affect the self-assembly of PAs. For instance, Zhou et al. introduced a negatively charged glutamic acid residue and asparagine residue into the N-terminal or C-terminal of the peptide PTP-7 (FLGALFKALSKLL), designing two anticancer peptides, EN (ENFLGALFKALSKLL) and NE (FLGALFKALSKLLNE) [32]. The obtained results have shown that the introduction of amino acids at different positions in the peptide chain changed the amphipathic and secondary structure content of PA. The peptide EN with glutamate and aspartate added at the N-terminus tended to form nanofibers. In contrast, the distance between the glutamic acid residue and the two lysine residues in the peptide NE was relatively short, which was conducive to stable intramolecular interactions and thus tended to form micelles. The obtained two PA nanostructures changed the time-action curve, improved the stability of serum, and revealed great clinical application prospects. Therefore, we suggest that the formation of PA nanostructures can also be regulated effectively by changing the position of adding amino acids when designing amphiphilic peptides.

Simultaneously changing the position and number of amino acids can also affect the self-assembly behavior of PAs. For instance, Pashuck et al. explored the effect of the PA sequence on the stiffness of formed PNFs [33]. The peptide composed of three parts, namely hydrophobic tail, ionizable side chains, and fragment of β-sheet, which promoted the formation of nanofibers. By changing the position and quantity of both lysine and alanine in the sequence, the mechanical properties of self-assembled PA structures were analyzed. It was found that the mechanical stiffness of the formed PA hydrogel could be increased by increasing the amount of lysine, while increasing the amount of alanine conversely decreased the mechanical stiffness of the hydrogel. It is ascribed to that lysine has the highest tendency to form the β-sheets, whereas alanine has a weaker tendency to form the β-sheets. In addition, it was found that the position of lysine and alanine in the peptide sequence also had a certain influence on the mechanical properties of the PA hydrogel. The closer the valine to the hydrophobic alkyl tail, the stiffer the resulting hydrogel was.

Changing the type of amino acids has also been considered as a way to control the amphiphilicity of peptides. Xu and co-workers showed that the short peptides of I_3K and L_3K have the ability to self-assemble into stable nanostructures [34]. Due to the slight difference in the structure of leucine and isoleucine, I_3K and L_3K self-assembled into different nanostructures under various driving forces in aqueous solution. Since isoleucine is a β-branched hydrophobic amino acid, it has a strong driving force to form β-sheets, so I_3K mainly exhibited a β-sheet structure in aqueous solution to form nanotubes with a diameter of 10 nm. While L_3K has no obvious β-sheet structure. It was driven by hydrophobic interactions to self-assemble into nanospheres with a diameter of about 10–15 nm in aqueous solution.

Finally, the rational exchange of D, L-chirality has been often used to enhance the stability of self-assembled peptides. Heterochiral co-assembly systems (racemic mixtures) containing both D- and L-isomers generally showed faster assembly kinetics and higher aggregation ability than enantiomers. Jeena et al. developed a heterochiral co-assembling amphiphilic peptide in mitochondria [35], as shown in Fig. 1.3b. In their study, a PA with mitochondrial targeting ability that coupled with triphenylphosphine (TPP) was designed, which contained two phenylalanines, named Mito-FF. Enantiomers could only assemble into nanofibers with a diameter of 9–11 nm. However, Mito-FF and its mirror-image structure (Mito-ff) could co-assemble in mitochondria into dispersed nanofibrils with a diameter of 100 nm and a length of 0.5–1 μm, ascribing to the higher binding energy between phenylalanine groups of opposite chirality.

1.4 Factors for Affecting PA Self-Assembly

1.4.1 Internal Interactions

Sun et al. explored the oligomeric structure and self-assembly mechanism of two short PAs, A_6K and V_6K [36]. The self-assembly behavior of both short peptides was affected by hydrogen bonds, hydrophobic interactions, and electrostatic interactions. The increased hydrophobicity made V_6K to show stronger self-assembly ability than A_6K. In addition, V_6K had a tendency to form compact β-sheet that can self-assemble into plate-like structure. However, due to the lack of hydrophobic interaction, A_6K presented a collapsed random coil structure under hydrogen bond interaction and only self-assembled into a monolayered sheet structure. In another case, Dasgupta et al. found that the hydrophobic interactions induced by the hydrophilic headgroup of PA and the number of hydrophobic groups affected the self-assembly of PA [37]. They explored the self-assembled nanostructure of simple double-chain PA, and the results proved that, in the self-assembly process of double-chain PA, although the hydrophilic head of PA tended to control the nanostructure of PA, the hydrophobic interaction still dominated. It tended to form β-sheet nanofibers firstly and then hydrogel, and the double-chain PA also exhibited cooperative self-assembly and improved aggregation behavior. This interesting self-assembly phenomenon provided useful information and inspiration for the development of functional biomaterials based on PAs.

Intrinsically disordered peptide amphiphiles (IDPAs) consist of an intrinsically ordered peptide bound to a hydrocarbon chain, resulting in an amphiphile with a polymeric head group and a hydrophobic anchor. Ehm et al. designed IDPA systems with four different amino acid sequences and observed the self-assembled nanostructures [38]. It was found that although the chain conformation of the peptide was disordered, the hydrophobic interactions between the head groups of the peptide affected the morphology of the self-assembled nanostructure. Structural phase transitions occurred in the number and length of PAs, which indicated that the mesoscopic structures (micelles, micellar tubes, or condensed phases) formed by the self-assembly of the sequence-designed IPDA and their structural transitions could be applied for the drug delivery systems. Alternatively, a functional peptide could be designed to render IDPA sensitive to enzymatic cleavage and induce an enzymatically activated phase transition, which enabled IDPA to serve as a nanocarrier that responsive to the metabolism of target sites. Similarly, Fu et al. explored the effect of hydrophobic interactions on the self-assembly behavior of PAs [39]. The effect of hydrophobic interactions was mainly adjusted by modifying the alkyl tail or peptide sequence. It was found that enhanced hydrophobic interactions led to the self-assembly of IDPA from open networks of secondary structures to closed cylindrical nanostructures containing β-sheets or random coils. In addition, since the hydrophobicity was affected by the system temperature, further studies revealed that the temperature also played an important role in regulating the formation of secondary structure within these self-assembled nanostructures.

In the process of molecular self-assembly, the anion-π interaction between the electron-deficient aromatic moieties of negatively charged groups is also important for final PA superstructures. For example, Yu et al. designed and synthesized three types of PAs [40], which contained a pentafluoro-phenylalanine at different positions in the main chain. The self-assembly of PAs and fatty acids that driven by the anion-π interaction was explored. When the aromatic unit was positioned close to the N-terminal of the peptide backbone near the hydrophobic core, a very strong anionic-π interaction between two components was generated to form nanofibers. The cylindrical morphology of PA was preserved due to the low content of dodecanoic acid that near the hydrophobic core. However, when the aromatic unit was far away from the hydrophobic core, the interaction with dodecanoic acid continued to increase, and the cylindrical structure was destroyed and transformed into a ribbon structure. Moreover, the adjusting of the ratio of dodecanoic acid to PA caused morphological changes of self-assembled PA nanostructures in this binary system.

1.4.2 Solution pH

Peptide self-assembly can be driven by various noncovalent interactions, including hydrogen bond, hydrophobic and electrostatic interactions, as well as others. These weak interactions are easily affected by environmental perturbations, such as the changes in solution pH, ionic strength, and temperature. In addition, some amino acids can provide functional groups for the metal complexation and enzymatic reactions. These intrinsic properties endow the peptide self-assembly with strong responsiveness to external factors. Therefore, the adjusting of solution conditions has become another important strategy to regulate the peptide self-assembly.

The change of solution pH will profoundly affect the side chains of amino acids through the protonation or deprotonation, resulting in the shift in the self-assembly pathway [41]. Ahmed and colleagues reported the self-assembly of Fmoc-protected lysine-based PAs that containing C_{16} chains to form hydrogels [42]. The hydrophobic part of the PA consisted of hexadecyl chains, which provided hydrophobic interactions for the hydrogelation of PA molecules. The free amine of the lysine side chain remained protonated under neutral conditions, thus acting as a hydrophilic group to increase the solubility of PA molecule in water. Under a suitable hydrophilic-lipophilic balance (HLB), driven by the combination of π-π stacking of Fmoc groups and hydrogen-bonding interactions, the PA molecules showed a tendency to aggregate and eventually self-assembled into helical PNFs efficiently. Interestingly, the chirality of the lysine residues affected the helical properties of the formed nanofibers. While the L-analog formed left-handed helical nanofibers, the D-enantiomer formed opposite right-handed helical nanofibers. However, this gelation behavior showed a strong pH dependence. When the pH of the solvent was >8, the free amine of the lysine side chain did not remain protonated, thus affecting the HLB of the PA molecule and the gelation behavior.

Hamley and co-workers investigated the self-assembly behavior of the surfactant-like peptide R_3L_{12} [43]. In aqueous solution, R_3L_{12} was able to self-assemble into nanostructures like nanotubes, tubular networks, and ordered lattice arrays through adjusting the solution pH. These structures consisted of α-helical antiparallel coil-coil peptide dimers that aligned perpendicular to the nanotube axis in a “crossed” nanotube configuration. The aggregation behavior was ascribed to the effects of the dimensionality and the balance of hydrophobic and electrostatic interactions.

Koc et al. explored supramolecular self-assembly of histidine-functionalized PA [44]. It was found that firstly the change of pH affected the noncovalent interactions of chiral PAs, thereby changing final self-assembled nanostructures. In an acidic environment, PAs self-assembled into thin-layer nanosheets mainly driven by hydrophobic interactions. With the change of pH, PA was mainly driven by hydrogen bond interaction and $\pi - \pi$ stacking of imidazole rings in alkaline environment, realizing the transition from thin-layer nanosheets to closed nanotubes. Meanwhile, the chirality of the amino acids also controlled the PA self-assembly behavior to a certain extent.

Cote et al. studied the effect of pH on the self-assembly behavior of the PA molecules carrying palmitoyl groups [1]. The self-assembly behavior of the peptide sequence $CH_3–(CH_2)_{14}CO–NH–I–A_3–E_4–CO–NH_2$ was studied. Affected by strong electrostatic repulsion, that is, under high pH environment, the side chain of glutamic acid was deprotonated, PAs presented a random coil arrangement and self-assembled into spherical micelles. However, affected by weak electrostatic repulsion, the glutamic acid side chain was fully protonated at low pH or in a neutral environment to form nanofibers. Meanwhile, it was found that the deprotonation of glutamic acid residues affected the pH of the solution. When the pH value was in the range of 6–7, the number of hydrogen bonds increased, and the peptide chain realized the conformation transition from random coil to β-sheet, which further affected the self-assembled structures.

Similarly, Liang et al. developed a pH-responsive PA for controllable drug release [45]. The PA has a sequence of DRQIKIWFQNRRMKWKK. At pH 7.4, the PA molecule exhibited a β-sheet conformation, which self-assembled into nanospheres with uniform size. Lysine and arginine were protonated in solution under mildly acidic conditions, for instance when the pH was 5.0. The secondary structure of the PA molecule was transformed, showing an α-helical conformation, and the self-assembled morphology changed from nanospheres to nanofibers. This reorganization of PA nanostructures under the pH stimulation could effectively realize controllable release of drugs into tumor cells and improve the treatment efficiency, showing new ideas for the design and applications of pH-responsive PAs.

1.4.3 Ionic Strength

The ionic strength is an important external factor that can affect the self-assembly of PAs. Iscen et al. explored how to use the Hofmeister effect to control the structure of PA nanofibers through atomic and molecular dynamics simulations [46]. Their results demonstrated that the self-assembly of PAs into supramolecular nanofibers could be tuned by adjusting the salt solution. The charged side-chain amino acid residues on the nanofibers generated strong electrostatic interactions with the anions in the salt solution, and different anions revealed different effects on the structure of PAs. For example, weakly hydrated ions (I^- and Br^-) would interact more easily with non-polar valine and alanine residues, which formed more stable β-sheet hydrophobic residues near the PNF core. However, strong hydrated ions (F^- and Cl^-) could interact with the side-chain amino groups of lysine to form salt bridges between lysine residues in adjacent PA chains. Therefore, the structure of PA nanofibers could be controlled by using different salt solutions, leading to the development of more stable supramolecular nanofibers.

Besides, the folding of PAs can be regulated by the incorporation with metallic ions. Inspired by controllable morphological changes of natural siderophores that secreted by amphiphilic marine bacteria caused by the metal coordination, Knight et al. designed hybrid peptide-polymer conjugates with different morphologies based on the coordination with metallic ions [47], with oligostyrene as hydrophobic tail and hexahistidine as hydrophilic chelating domain, and the thiol-maleimide reaction was used to couple the peptide and oligostyrene. Finally, the self-assembly of the peptide-polymer conjugate in different metal salt solutions was observed. It was found that in the absence of transition metals, PAs self-assembled into vesicles. However, in the presence of Zn^{2+}, due to the coordination reaction, PAs finally aggregated into particles. This situation has also been observed in the salt solution of Co^{2+} and Cu^{2+}. In addition, metal ion-induced micelles were found by adding Ni^{2+} and Cd^{2+}, and vesicles were formed when the PAs were coordinated with Mn^{2+}. Based on the obtained results, it was concluded that the coordination between transition metals and PAs changed the self-assembled structures of PAs, which were affected by the properties of the added transition metals. This study provided great inspiration on the design and synthesis of stimuli-responsive PA-based nanomaterials.

1.4.4 Temperature

Typically, the temperature change can trigger the secondary structure transitions of temperature-responsive peptides, thereby affecting their self-assembled nanostructures. For instance, Han et al. explored the self-assembly of thermo-responsive PAs [48], in which they chose the thermo-sensitive PA, elastin-like peptide (ELP). The ELP molecule composed of the repeating pentapeptide sequence VPGXG, and X was the guest residue, which could be any amino acid except proline. When the temperature of the solution was increased, the ELP molecules were triggered by the temperature, the hydrophobic valine side chain was dehydrated, and the hydrophobic activity increased, which promoted the self-assembly of ELP into spherical micelles in the solution. Silica protein R5 peptide was introduced at the hydrophilic end of the ELP co-block. The silica underwent local aggregation without affecting the spherical micelle structure to form nearly monodispersed hybrid ELP-silica particles. This temperature-controlled hybrid nanoparticle exhibited potential application in biomedical fields.

In a similar study, Cao et al. further introduced the VPGXG peptide sequence into a PA molecule to study the effect of the temperature on the self-assembly behavior of the PA [49]. Studies have shown that the change of temperature not only affected the self-assembly process, but also had a certain control effect on the self-assembly pathway. PA molecules self-assembled into short and smooth nanofibers at 20 °C, while the self-assembled morphology was affected with increasing temperature, transforming into long fibers with a length of several μm at 80 °C. The surface roughness and diameter of the nanofibers generated at both temperatures were quite different, and the increase of temperature led to the formation of more β-sheets, which caused the peptide chain to undergo a conformational transition. It was deduced that the nanofibers may come from different self-assembly pathways. Interestingly, the amount of the introduced VPGXG peptide sequence also significantly affected the self-assembled morphology. Thus, functional peptide materials could be efficiently constructed by introducing thermo-sensitive sequences into the self-assembling peptides.

1.4.5 Other Factors

The introduction of enzymes to peptide systems also induced the self-assembly or dis-assembly of peptides [50]. For instance, Bai et al. reported the design and self-assembly of PA, Ac-VVVVVVKKK-NH_2 (V_6K_3), which underwent a structural transformation induced by plasma amine oxidase (PAO) [51]. The PA consisted of a hydrophobic domain containing six valines and a hydrophilic domain containing three lysines. Its N-terminus was protected by an acetyl group to prevent the degradation by enzymes, such as dipeptidyl peptidase IV. Under the action of hydrogen bonds, van der Waals force, and hydrophobic interactions, the self-assembly of V_6K_3 peptide formed spherical nanoparticles. Under the induction of PAO, the created spherical nanoparticles were destroyed and transformed into nanofibers, as shown in Fig. 1.4a. The secondary structure of V_6K_3 changed and underwent a geometric transformation based on enzymatic reaction. Interestingly, the lysine residues provided positive charges, while the positive charges carried by the PA V6K3 decreased after the addition of PAO. However, the bactericidal performance of V_6K_3 increased instead of decreasing, indicating that the self-assembled structure was also an important factor affecting antibacterial performance of peptide materials.

In another work by Bai et al., an amphiphilic peptide A_6K_2 was designed, which could undergo structural transformation under the catalysis of lysyl oxidase (LO) and PAO [52]. Positively charged A_6K_2 self-assembled into stable nanovesicles in the HEPES buffer. In the presence of enzymes, the lysine residues in the peptide were oxidized by LO or PAO, and the nanovesicles slowly dis-assembled and gradually formed nanofibers, which triggered the conversion of random coil to β-sheet conformation. Lipid-soluble DOX was then encapsulated into the self-assembled

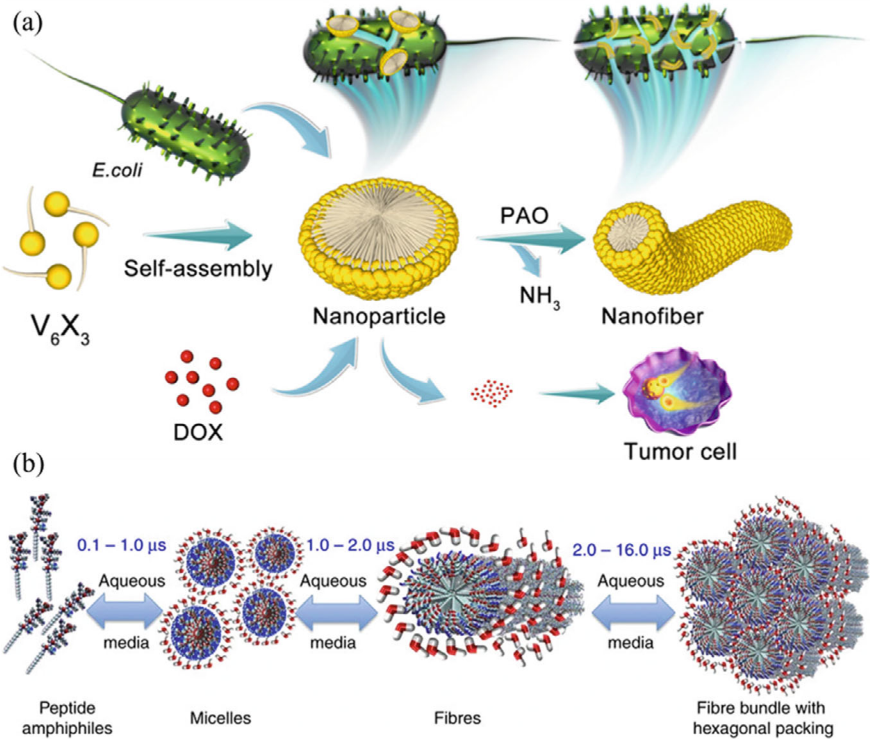

Fig. 1.4 **a** PAO-induced nanoparticle-to-nanofiber geometric transition of V6K3. Reproduced with the permission from Ref. [51]. Copyright 2020, American Chemical Society. **b** Schematic of the various stages involved in PA self-assembly. Reproduced with the permission from Ref. [54]. Copyright 2016, Springer

A_6K_2 nanovesicles as a model drug, and the destruction of the vesicles induced by LO or PAO could promote the drug release.

Nanostructures on different substrates are affected by the local surface concentration and drying method, showing different morphologies. Liao et al. studied the self-assembly behavior of small PA (NapFFKYp) both in solution and on substrates [53]. Studies have shown that PA self-assembled into nanofibers through a nucleation process in solution and further aggregated to form higher-order nanofibers. Subsequently, the self-assembly of PA on mica, highly oriented pyrolytic graphite (HOPG), and polystyrene (PS) films were explored. The local concentrations were different, resulting in the formation of nanosheets with different thicknesses. Meanwhile, the addition of water realized the transformation from nanoflakes to nanofibers. It was clear that the addition of water destroyed the original highly ordered β-sheet layer, and the hydrophilic ends tended to be surrounded by water, eventually forming nanofibers. Finally, molecular dynamics (MD) simulations revealed that the hydrophobicity and ion-ion interactions played the main forces for driving the formation of various nanostructures. The chemical properties and molecular details of water molecules also played a key role in the assembly mechanism and dynamic equilibrium between the phases during the self-assembly of PAs. In addition, the local interfacial ordering of water played a key role in determining the assembly mechanism and dynamic balance among the various stages in the self-assembly process.

Deshmukh et al. explored the role of water molecules in the self-assembly of PAs through multilevel coupled atom-CG MD simulations [54]. The structural formula of the PA was C_{16}–AHL_3K_3–CO_2H, in which C_{16} was connected to the hydrophilic sequence as a hydrophobic tail. Studies have shown that the local ordering of water molecules had a certain influence on early formation of micellar fiber. The order of water molecules near hydrophobic amino acids was broken, and the water cages were broken, which promoted the aggregation of randomly dispersed PAs. The structural order of water molecules near the hydrophilic group was enhanced, driving the transition from micelles to nanofibers, as shown in Fig. 1.4b. During the self-assembly process, water molecules became increasingly ordered, promoting the early hierarchical self-assembly of PAs.

1.5 Conclusion

In summary, we focused on the design and self-assembly of PAs in this chapter. Firstly, some design methods and self-assembly behaviors of PAs were analyzed and discussed. Secondly, we analyzed several strategies to change the amphiphilicity of PAs, such as regulating the number of amino acids in the peptide sequence, changing the relative position and type of amino acids, and changing the chirality of amino acids. Finally, we discussed the influence of environmental factors, such as the interactions, pH, ionic strength, and temperature on the nanostructures of self-assembled PAs.

This chapter provides a reference for designing the sequence of PAs. The design and synthesis of PAs are always performed for specific biomedical and nanotechnological applications. By understanding the preconditions of specific applications and referring to the influences of various factors on the PA self-assembly, PAs with specific structure and function can be designed effectively. We believe that through continuous understanding on the mechanisms of the PA self-assembly, it is possible to develop functional PAs with higher efficacy in the required fields in the future and expand their applications in materials science and nanotechnology.

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