

Chapter 2

Advantages of Self-assembled Supramolecular Polymers Toward Biological Applications

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Abstract Supramolecular self-assembly provides a means of achieving “bottom-up” fabrication of nanoscale materials. Their mechanical properties and functionality arise from the assembly of relatively simple molecular building blocks. These materials have selective affinity to different interfaces, high capacity for interfacial adsorption, nanostructure, and spontaneous formation of unique nano-self-assemblies which exhibit remarkable simplicity and biocompatibility. Due to these attractive features, supramolecular nanostructures, particularly peptide-based, have recently been explored as effective nanomaterials in applications ranging from controlled release and drug delivery, nano-fabrication, skin care, biomineralization, sensing, antimicrobial materials, and tissue engineering. This range of applications is facilitated by the diverse primary sequences of the short peptides, which can be either biomimetic or de novo designed. Thus, their self-assembling mechanistic processes and nanostructures also vary enormously. This chapter highlights recent advances in studying self-assembled peptide systems, focusing on the formation of different nanostructures and their applications in diverse fields.

Keywords Self-assembly • Hydrogel • Peptides • Nanostructures • Supramolecular polymers

List of Abbreviations

SAP	Self-assembling peptide
CPTNs	Cyclic peptide nanotubes
CPs	Cyclic peptides
PAs	Peptide amphiphiles
RGD	Arginine–glycine–aspartic acid
CryoTEM	Cryogenic transmission electron microscopy
CMC	Critical micelle concentration

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DOX	Drug doxorubicin
CPP	Cell penetrating peptide
GQDs	Graphene quantum dots
FF	Diphenylalanine
Fmoc	Fluorenylmethoxycarbonyl
Boc-FF	Tert-Butyloxycarbonyl-diphenylalanine

2.1 Introduction

2.1.1 *Self-assembly in Nature*

Nature endows intricate mysteries regarding biologic processes underlying the formation of a wide variety of complex biological structures. Thus, it has been our greatest “teacher” of all times. Do we ever think of what it takes to turn an egg to an entire animal? Or how a densely packed group of hexagonal cells comprise multiple honeycombs parallel to each other, with a relatively uniform bee space? How does a seed turn into a single tree and the trees to a forest? Or how do sand grains collectively form a sand-dune or a desert? How, depending on different environmental circumstances, can simple water molecules take the form of rain to ocean, ice cube to iceberg, steam to cloud, and super-cooled cloud droplets freezing into magnificent snowflakes?

Nature accomplishes all these phenomena with high level of precision and complexity. It offers “bottom-up” nano-fabrication, constructing materials atom by atom or molecule by molecule to produce beautiful supramolecular self-assembled architectures. Self-assembly is a ubiquitous process in biology where it plays numerous important roles and underlies the formation of a wide variety of complex biological structures. Phospholipid molecules spontaneously arrange themselves in exceptionally ordered structures to form cell membranes and compartmentalization of elements within these membranes, a process which has probably led to the foundation of cells and thus to “LIFE.” Protein folding, the formation of DNA double helix, morphogenesis, etc., are some of the most complex, spontaneously formed self-assembled systems. One of the easiest modes of understanding the intricacies of living systems is to explore their components. The basis underlying such processes lies in the tendency of single units to interact with each other to create a unique, complex, but highly organized system.

Over the past two decades, materials scientists have aspired to exploit nature’s self-assembly principles to develop biomimicking systems. Toward this goal, both biological and synthetic building blocks have been subject of extensive research. In fact, molecular self-assembly has become increasingly important for the development of biomaterials as it offers a great platform for constructing materials with high level of precision and complexity, while integrating order and dynamics, to

achieve functions such as stimuli-responsiveness, adaptation, recognition, transport, and catalysis. The importance of peptide self-assembling building blocks has been recognized in the last years, as they offer a great diversity of biochemical (specificity, intrinsic bioactivity, biodegradability) and physical (small size, conformation) properties to form self-assembled structures with different molecular configurations.

This chapter provides an overview of the design principles of peptide self-assembly and illustrates how these principles have been applied to manipulate self-assembly across the scales. Applications of self-assembling peptides as nanobiomaterials, including carriers for drug delivery, hydrogels for cell culture and tissue repair, are also described.

2.1.2 Self-assembly and Supramolecular Chemistry

Molecular self-assembly is a spontaneous organization of molecular units into ordered structures [1]. The assembly process is facilitated by recognition and association of molecules, controlled by the balance of attractive and repulsive forces within and between them, leading to weak non-covalent intra- and inter-molecular interactions including Van der Waals, electrostatic, hydrogen bonding, and π - π stacking interactions [2, 3]. Together, these weak interactions form the basis for fabrication of very stable supramolecular architectures and bio-inspired nanomaterials with chemical complementarity and structural compatibility [4]. The arrangement of the nanostructures depends on molecular composition, assembly kinetics, and variations in the assembly environment (pH, solvent, co-assembling molecules, temperature, and ionic strength) [5, 6].

Self-assembly underlies the generation of many biological nanostructures. DNA double helix formation through hydrogen bonding interactions between nucleotide bases, formation of tertiary or quaternary protein structures through folding of a polypeptide chain, and the formation of cell membranes upon self-assembly of phospholipids are some of the most straight-forward and extensively studied self-assembled structures in a biological system.

The understanding of the spontaneous molecular self-assembly process, along with advances in the design and characterization of such self-organization principles in molecular engineering, have led to the fabrication of new materials using natural building blocks, such as phospholipids, oligosaccharides, oligonucleotides, proteins, and peptides. Amongst the wide variety of molecules often used in this nanotechnology field, several unique properties make peptides, peptide derivatives and proteins particularly attractive building blocks for the construction of supramolecular materials. First, they display an inherent ability to self-organize into well-defined structures. Second, they can deliver potent and selective biological signals to cells, thus enabling to manage varying cellular responses. Third, they can be fabricated by a number of means, including solid- and liquid-phase chemistry, biocatalysis, metabolic engineering, and recombinant expression biotechnologies.

Peptide chemistry is well-established, highly reproducible, and allows easy incorporation of non-peptidic moieties [7, 8]. In other words, peptides are easily accessible not only to chemists, but also to biologists, biochemists, and materials scientists who may not be capable of overcoming the synthetic challenges posed by other non-peptidic small molecules. Peptides thus seem ideal candidates for biological applications.

Self-assembling peptide (SAP) systems involve synthetic scaffolds capable of presenting multiple cell-interactive components in spatially resolved networks via supramolecular self-assembly. In addition, peptides have become known as immensely useful building blocks for the formation of self-assembled nanostructures in medical applications due to their biocompatibility, biodegradability, and versatility. They can be used for drug delivery, tissue engineering, scaffolds for regenerative medicine, matrices for cell cultures, antimicrobial agents, imaging tools, energy storage, biomineralization, and membrane protein stabilization. These applications employ self-assembled peptides with bioinspired nanostructures showing different properties, including nanotubes, nanofibers, nanospheres, nanobelts, and hydrogels. A number of peptide-based building blocks, such as amphiphilic peptides, surfactant-like oligopeptides, and aromatic dipeptides, have been designed and developed for generating supramolecular structures and their possible applications in biology and nanotechnology are explored. SAP systems are also capable of displaying functional amino acid sequences or chemical groups on the surface of their self-assembled fibers and these peptides can also serve as anchors for different ligands.

2.2 Supramolecular Materials

2.2.1 *Cyclic Peptide Nanotubes*

2.2.1.1 Design of Cyclic Peptide Nanotubes

In recent years, considerable effort has been devoted to the preparation of artificial nanotubular materials. One of the most successful approaches for the construction of non-covalently bonded nanotube entities is the self-assembly of cyclic polypeptides in stacks that are stabilized by hydrogen bonds.

In 1993, cyclic peptide nanotubes (CPTNs) were presented as a new class of organic nanotubes in a pioneering work by Ghadiri et al. CPTNs form hollow tubular nanostructures by self-assembly containing even numbers of alternating D- and L-amino acids [9]. This unique architecture results in flat ring-shaped subunits stacked together into a β -sheet conformation through intermolecular hydrogen bonds. The closed cycle and the alternating D- and L-conformations direct the side chains outward of the ring and the backbone amides approximately perpendicular to the ring's plane. The internal diameter of the nanotubes ranges between 7 and 8 Å and can

be controlled by changing the number of the amino acids in the cyclic peptide sequence. By tailoring the chemical structure of the cyclic peptide moieties, the self-assembled supramolecular architectures can be adjusted to meet the requirements of a variety of applications, including antibacterial agents, stimuli-responsive nanomaterials, ion channeling, and ion sensing.

2.2.1.2 Application of Cyclic Peptide Nanotubes

(1) Antimicrobial agents

CPNTs have been of particular interest as antibacterial agents [10, 11]. They act on bacterial membranes and other generalized targets, thus making bacterial resistance unlikely [12]. The mechanism of their antibacterial activity includes binding to the target membrane, in which they transform their structure [13, 14]. At a certain threshold concentration, CPNTs permeabilize the membrane, either by forming a discrete pore or by disrupting the bilayer structure [15]. Membrane selectivity, a major requirement for antimicrobial materials, was assessed by subjecting the cyclic peptide to a hemolysis assay.

The antibacterial activity of CPNTs is governed by several factors including the ring size of the cyclic peptide being either six or eight amino acids, the type of amino acids composing in the peptide, and the type and number of basic amino acids in the peptide sequence [16].

In one early example, Ghadiri's group showed that octameric or hexameric alternating D,L-CPNTs cause permeabilization of the bacterial membrane, thereby showing antimicrobial activity [17]. Selective activity against gram positive (*S. aureus*, MRSA) or gram negative (*E. coli*) bacteria compared to mammalian cells was demonstrated. They also established that control peptides comprising linear sequences did not have antibacterial activity when compared to their cyclic counterparts [17]. In addition, hexameric cyclic peptides were shown to be less effective antibacterial materials than octameric CPNTs. They also found that increasing the number of basic residues in the cyclic peptide increased the antibacterial activity, while switching the chirality of the basic amino acids had no significant effect on either antibacterial or haemolytic activity. Introduction of histidine as a basic residue in the hexa- or octameric cyclic peptide, however, resulted in a loss of broad-spectrum antibacterial activity, along with an increase in haemolytic activity, and thus loss of membrane selectivity. In a recent study, the cyclic peptide Labaditin was proven as highly efficient in killing *S. aureus*. With assays of membrane permeability, it was found that Labaditin induced leakage in large unilamellar vesicles, via formation of pores [11].

(2) Ion channels

The ability of cyclic peptides to integrate into lipid bilayers and disrupt membranes makes them suitable for ion channeling [18]. Ghadiri's group elaborated this fact

and have constructed artificial ion channel models that exploit the self-assembly of conformationally flat cyclic peptides (CPs) into supramolecular nanotubes [19]. They have also designed a cyclic peptide nanotube based on eight amino acids which was shown to serve as an artificial transmembrane ion channel and display transport activities for potassium and sodium [20]. The peptide incorporated leucine and tryptophan residues to favor its partitioning into lipid bilayers. The pores formed spontaneously upon addition of the peptide to an aqueous liposome dispersion. Single-channel conductance and proton efflux (pH-sensitive dye fluorescence) confirmed the presence of ion channels [20]. Another cyclic peptide composed of cyclo[-Trp-Dap-Leu-D-Ala-Trp-Ser-Val-D-Ala-Trp-Ser-Ile-Gly-] was found to be capable of forming artificial transmembrane ion channels by self-assembly of planar peptide rings, with hydrophilic groups arrayed in the interior of the channel [21].

(3) Ion sensors

The self-assembly of cyclic peptides into tubular channels in organosulfur self-assembled monolayers on gold films enables the construction of diffusion-limited size-selective sensors [22], which have been used to probe redox ion complexes in solution. Through measurements of redox activity, Motesharei and Ghadiri showed that negatively charged $[\text{Fe}(\text{CN})_6]^{3-}$ and positively charged $[\text{Ru}(\text{NH}_3)_6]^{3+}$ complexes were able to traverse the channel lumen. However, upon the addition of the larger $[\text{Mo}(\text{CN})_8]^{4-}$ anion, no redox activity was observed. In addition, selectivity was confirmed when a mixture of $[\text{Fe}(\text{CN})_6]^{3-}$ and $[\text{Mo}(\text{CN})_8]^{4-}$ was added to self-assembled monolayers [22]. In the recent works, a new self-assembly process based on an α,γ -cyclic peptide was utilized to design molecular rotors ion sensors [23]. In another study, a phosphorylated cyclic peptide was used as a fluorescent sensor for the detection of uranyl ions with high selectivity and sensitivity [24].

(4) Gene delivery

CPNTs have been used as dose-dependent inhibitors of adenovirus mediated gene delivery. Horne et al. showed that the designed cyclic D,L- α -peptides can rapidly permeate selected cellular membranes and counteract the development of a low pH environment inside endosomes [25]. The CNPTs could potentially prevent adenovirus infection, thus showing potential supramolecular approach toward the design and discovery of broad-spectrum antiviral agents.

(5) Responsive supramolecular polymers

The transition between intermolecular and intramolecular dimerization could be controlled using N-methylated peptides covalently linked together with an azobenzene linker. Upon irradiation at 366 nm, the azobenzene switches from the E to the Z isomer, leading to a switch from intermolecular dimers, which form a supramolecular polymer, to discrete intramolecular dimers [26]. Steinem et al. reported that the supramolecular polymers undergo reversible structural changes at the air–water interface upon UV or visible light irradiation. Such changes could provide a new route toward the design of novel photoactive materials [27].

2.2.2 Peptide Amphiphiles

Peptide amphiphiles (PAs) are composed of oligopeptides consisting of an N-terminal alkyl tail, a β -sheet-forming central segment, and a C-terminal functional segment representing a flexible platform for incorporating a variety of different molecular features [28]. These molecules generally assemble into high aspect ratio rods/cylinders with a hydrophobic core consisting of 12–16 carbon alkyl tails and the peptide presented radially from the core. Formation of rods by PAs is driven by a combination of both the hydrophobic interaction between the alkyl tails and the hydrogen bonding of the peptides, hence providing a β -sheet conformation [2]. PAs have been designed with increasingly complex and bulky functional domains such as fluorophores, branched with two arginine–glycine–aspartic acid (RGD) ligands or one YIGSR and one IKVAV ligand, cyclic RGD ligands, and others [28]. Stability can be provided by modifying the N-terminal alkyl by the inclusion of diacetylene groups, whereas flexibility has been demonstrated by incorporating proteolytically susceptible amino acid sequences in the central portion of the PAs [29]. The rigidity of the rods can also be altered by the addition of a phospholipid. A low percentage of phospholipids allows the rheological properties of the gel to be altered with a slight increase in the mechanical properties, possibly due to a more optimal geometry of interactions between PA molecules for hydrogen bonding [30]. Thus PAs, owing to their predictable self-assembly, their ease of synthesis, and their capacity for incorporating a wide variety of functional components and mechanical properties, have been used for a number of interesting applications.

Stupp and coworkers have developed a series of lipid-peptide molecules comprising a hydrocarbon chain (e.g., palmitoyl) covalently attached to an amphiphilic peptide (e.g., VnAnEn) which is able to form β -sheet-rich supramolecular structures. When dispersed in water, these PAs formed hydrogels at concentrations as low as 1% (w/v) in the presence of calcium ions that triggered gelation through charge screening. Interestingly, these PAs kept their hydrogel-forming capacity even after covalent conjugation of dexamethasone or prodan to the peptide moieties via acid-cleavable hydrazone bond [31, 32]. This feature makes these PAs a versatile system for sustained release of a wide range of medicines. While in most cases, PAs were utilized for drug delivery in hydrogel forms, in a recent study, PA fibers conjugated to a collagen binding peptide showed promising results for targeted delivery to an injured artery via systemic administration following vascular intervention. Importantly, findings indicated that applying the specific targeting ligands in combination with fibrous morphology was crucial to get the optimal binding at the site of interest in the vasculature [33].

Recently, Deshmukh et al. have shown the role of water molecules in the dynamic equilibrium of micelle-fiber formation in self-assembly of PAs [34]. The various stages of self-assembly from micelles, fibers, and bundled fibers take place

at a particular time scale (Fig. 2.1a), thus providing extensive insights into early fiber formation and the role of solvent in the process of self-assembly [34]. Moreover, the ability of the fibers to structurally adapt to bind important bioactive targets was recently demonstrated [35]. PA molecules formed nanofibers in water, with a diameter of approximately 7 nm and lengths in the range of micrometers, as observed by cryogenic transmission electron microscopy (CryoTEM; Fig. 2.1b–c). Amphiphiles were fluorescently labeled with Cy3 and Cy5 fluorophores and the distribution of dyes integrated into initially single-color nanofibres was quantified using correlative image analysis. Fluorescently labeled nanofibers revealed similar morphology to that of non-labeled counterparts, as shown by cryoTEM (Fig. 2.1d). Diffraction-limited fluorescence microscopy images of Cy3- (Fig. 2.1e) and Cy5-labeled (Fig. 2.1f) PA nanofibers show similar morphology.

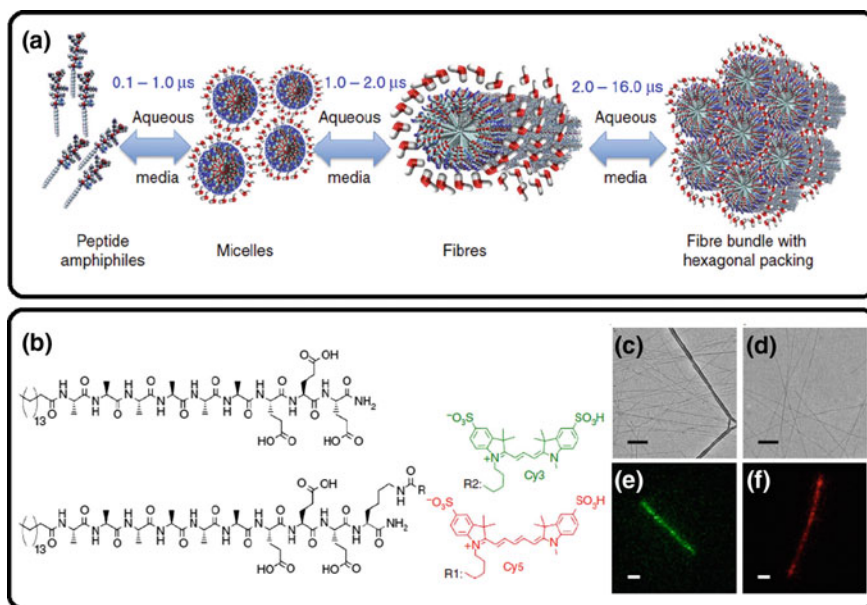


Fig. 2.1 Peptide amphiphiles self-assemble into various morphological structures. **a** Schematic representation of the various stages involved in PA self-assembly with the timescale denoted in blue (Reprinted with permission from Ref. [34]. Copyright 2016, Macmillan Publishers Limited, part of Springer Nature. **b** Molecular structure of non-labeled PA and PA molecules labeled with photo-switchable sulfonated cyanine dyes, namely Cy3 (green) and Cy5 (red). **c–d** CryoTEM images of nanofibers self-assembled in 150 mM NaCl, pH 7.5, **c** from non-labeled PA alone and **d** from a molecular mixture of non-labeled and Cy5-labeled PAs (scale bar, 200 nm). **e–f** Diffraction-limited fluorescence microscopy images of Cy3- (**e**) and Cy5- (**f**) labeled PA nanofibers (scale bar, 1 μm) (Reprinted with permission from Ref. [35] Copyright 2016, Nature Publishing Group, Macmillan Publishers Limited)

2.2.3 *Surfactant-Like Peptides*

Surfactants are defined as materials that can greatly decrease the surface tension of solvents when used at very low concentrations [36]. A typical surfactant-like peptide molecule consists of two parts: a hydrophobic tail composed of several consecutive hydrophobic amino acids and a hydrophilic head composed of one or two hydrophilic amino acids. Various surfactant-like peptides can be designed by selecting different hydrophobic or hydrophilic amino acids. For example, the hydrophilic head can be designed as positively charged Arg, Lys, and His, or negatively charged Asp and Glu, producing cationic or anionic surfactant-like peptides, respectively. On the other hand, the hydrophobic tail can be designed by choosing different hydrophobic amino acids such as Gly, Ala, Val, Leu, and Ile with different levels of hydrophobicity, so that the overall hydrophobicity of a surfactant-like peptide is controlled. The design of the typical surfactant-like peptide is based not only on the selection of amino acids, but also on the position of the hydrophilic head which can be set at either the C- or N-terminus [37]. The length of the surfactant-like peptide is controlled by the number of hydrophobic amino acids in the tail.

The assembly mechanism of the peptides leads to different nanostructures used for different applications. One self-assembly model of surfactant-like peptides is based on a tail-to-tail alignment to form bilayer structures which further form nanotubes and nanovesicles. In addition to forming a tail-to-tail bilayer structure, traditional surfactants can also form micelles by packing the tails in a hydrophobic core and exposing the hydrophilic heads outside. This kind of self-assembly model has also been observed for surfactant-like peptides, which can form nanofibers instead of nanotubes or nanovesicles [38]. Cationic surfactant-like peptides can form nanofibers, nanorods, and nanospheres with various lengths by packing in the unique orientations as described above.

Surfactants, as their name suggests, have a general tendency of moving to the surface (air/water) or interface (oil/water), and thus they are also known as “surface active agents.” The dual characteristics of surfactant molecules show a wide range of properties mainly connected to two key features, namely adsorption at interfaces and self-assembly in bulk solution. Structure–function relationships on the surface and solution properties have been investigated for a wide range of surfactant types with the aim of utilizing them toward relevant applications. Depending on the nature of the hydrophilic moiety ensuring the water affinity of the molecule, surfactant-like peptides can be categorized into anionic, cationic, nonionic and zwitterionic.

2.2.3.1 *Anionic Surfactants*

Historically, anionic surfactants are the earliest and the most common surfactants. They are surface active substances in which, e.g., one hydrophobic group is

connected with one or two hydrophilic groups. In aqueous solution, dissociation occurs into an anion and a cation. The anion is the carrier of the surface active properties. The ionized moiety can be a carboxylate, sulfate, sulfonate, or phosphate. Surfactants can be used as detergents (alkylbenzene sulfonates), soaps (carboxylic acids), foaming agents (lauryl sulfate), wetting agents (di-alkyl sulfo-succinate), and dispersants (lignosulfonates).

2.2.3.2 Cationic Surfactants

Cationic surfactants, which also contain a hydrophobic hydrocarbon group and one or several hydrophilic groups, also dissociate into cation and anion in aqueous medium. Here, however, the cation is the carrier of the surface active properties. Cationic surfactants are characterized by their very high substantivity on various substrates, especially the negatively charged ones, and by the subsequent surface modifications. They are often used as conditioning agents in fabric care and hair products. They are also used as germicidal agents (bactericides and fungicides) and to produce antistatic and hydrophobic effects, and are thus commercially valuable as corrosion inhibitors.

2.2.3.3 Nonionic Surfactants

Nonionic surfactants are surface active substances which do not dissociate into ions in aqueous solutions. The solubility of these substances in water is provided by polar groups such as polyglycol ether groups or polyol groups.

2.2.3.4 Amphoteric or Zwitterionic Surfactants

Amphoteric or zwitterionic surfactants are characterized by one anionic and one cationic functional groups whose dominance is usually regulated by the pH, namely anionic in alkaline pH and cationic in acidic pH. Near the isoelectric point, these surfactants display both charges and are amphoteric in nature with a minimum of interfacial activity and a maximum of water solubility. Amphoteric surfactants, particularly those composed of amino acids, are quite biocompatible and used in pharmaceuticals and cosmetics.

2.2.3.5 Gemini Surfactants

Over the past two decades, dimeric or gemini surfactants attracted considerable interest aiming at developing “next-generation” high-quality surfactants [39]. These surfactants are constructed by linking two monomeric surfactants with a spacer at the level of or in close vicinity to the head groups. They have many unique

properties that are superior to those of their corresponding monomers, such as significantly lower critical micelle concentration (CMC), high surface activity, low Krafft temperature, unusual rheological properties, better wetting ability, etc. Their unique aggregate morphologies in solution are also of intense research interest [40]. Gemini surfactants are used as promising surfactants in industrial detergency, as nano-templating agents, as skin care agent, and for catalysis [41].

2.2.3.6 Applications of Surfactant-like Peptides

(1) Stabilization of membrane proteins

Surfactant-like peptides have shown promising potential in the study of membrane proteins. About one-third of all cellular proteins are membrane proteins, which contain at least one transmembrane domain and play vital roles in every aspect of cellular activities, including cell signaling, cell migration and movement, energy transformation, and substance transport [42]. However, due to their unstable nature, stabilization is required for analysis. In the past decades, various traditional surfactants, such as detergents and lipids, were used for stabilization, purification, and crystallization of membrane proteins. However, due to the complexity of membrane protein–detergent–lipid interactions, their efficacy is still lacking. In contrast, based on their molecular structure, surfactant-like peptides can bind to the hydrophobic section of a membrane protein through their hydrophobic tails and sequester it from the water, thus preventing its denaturation [43].

(2) Drug and gene delivery

Since surfactant-like peptide molecules can be easily designed and modified to form various nanostructures, they can be easily tailored for drug or gene delivery. The hydrophobic core within the nanostructure can potentially encapsulate water-insoluble molecules and deliver drugs and other biological molecules. Moreover, the hydrophilic head can be modified with functional groups for cell-targeting.

Surfactant-like peptides have been shown to form vesicular structures, depending on the primary sequence, peptide concentration, pH, and ionic strength of the dispersing media [44–46]. For example, the SA2 peptide (Ac-AAVVLLWEE) forms discrete nanovesicles with a radius of 60 nm when dispersed in aqueous media at physiological pH. The formed peptide vesicles precipitate out of solution at pH values below the pK_a of the glutamic acid side groups, which could be fully reversed when the pH was raised again to 7.4 [45]. SA2 peptide vesicles can be loaded with a photosensitizer with virtually no water solubility. Incubation of different cultured cells (HUVECS, COS-7, and C26) with SA2 peptide vesicles loaded with this photosensitizer resulted in accumulation of the photosensitizer inside the cells. Upon illumination to excite the delivered photosensitizer, concentration-dependent cytotoxicity was observed, in contrast to non-illuminated control cells [46].

Recently, self-assembled polymeric micelles from amphiphilic copolymers and a hydrophobic tail were investigated as nanocarrier systems for the controlled release of various anticancer drugs [47–49]. In an *in vitro* study, micelles were loaded with ibuprofen and the anticancer drug doxorubicin (DOX) and the sustained release behavior was examined [47]. Due to the incorporation of targeted RGD sequences and the cell penetrating peptide (CPP) residue octa-arginine (R(8)), the micelles could be specifically recognized by cancer cells, as well as be efficiently transported through the cell membrane. The loaded micelles showed high phototoxicity against cancer cells, indicating a powerful potential for effective photodynamic therapy. Furthermore, due to the low cytotoxicity of the peptide against both HeLa and 293T cell lines, the surfactant-like peptide developed in this study may be promising for targeted drug delivery in clinical application [47]. Cui et al. further synthesized reduction-sensitive micelles for enhanced drug delivery effect. These micelles, are stimuli-sensitive and may be triggered by changes in temperature, pH, light, magnetic field, ultrasound, and redox potential, and are thus considered “smart drug carriers” for tumor drug delivery. Upon reaching the target tumor cells, the drug-loaded micelles can be intracellularly localized and subsequently aroused by stimulus to rapidly release the drugs due to the transformation of the chemical structures or the physical properties of the carriers, resulting in aggressive activity inside tumor cells, enhanced therapeutic efficacy, and relatively few side effects. The reduction-sensitive polymeric micelles containing disulfide bonds have been extensively studied for tumor targeting due to the high difference in the redox potential between the mildly oxidizing extracellular milieu and the reducing intracellular fluids. Moreover, tumor tissues are highly reducing and hypoxic compared to normal tissues, with at least fourfold higher concentrations of reducing agents in tumor tissues [50]. The micelles developed by Cui et al. were based on the amphiphilic polymer mPEG-S-S-C16 synthesized by conjugating the hydrophilic mPEG with the hydrophobic alkyl chain by a reduction-responsive disulfide bond followed by self-assembly into micellar aggregates in aqueous solution. These micelles efficiently delivered DOX to the cell nuclei and showed enhanced drug effects when compared to control micelles without a disulfide bond [48].

Surfactant-like peptides have been suggested as DNA delivery systems for gene therapy. Due to the ability of cationic surfactant-like peptides to self-assemble into cationic micelles, the negatively charged DNA binding efficiency was increased [51]. Furthermore, co-delivery of DOX with luciferase reporter gene and p53 gene was demonstrated using micelles [52].

Gemini surfactants have also been proposed as candidates for gene therapy toward mitochondrial diseases. They were shown to successfully deliver a plasmid DNA construct designed by including a codon, which codes for an amino acid only if read by the mitochondrial ribosomes, thus bearing the potential to transform the therapeutic landscape of mitochondrial genetic diseases [53]. Various types of gemini surfactants have been designed for gene therapy for the treatment of various

diseases. To this end, they have been utilized as candidates for the formation of non-viral vectors. The transfection efficiency of different types of gemini surfactants has been evaluated in a recent review [54].

(3) Tissue engineering

Surfactant-like peptides can be used as surface modifying molecules for scaffold-free tissue engineering by promoting cell adhesion and growth. A6K, a cationic surfactant-like peptide, was shown to self-assemble on mica surface to form a monolayer, thus turning the surface into a hydrophobic one, which is suitable for cell adhesion and growth. Along with the growth of cultured cells, A6K peptide composed of natural L-amino acids could be gradually biodegraded, and the hydrophilic mica surface could be re-exposed, thereby allowing for an easy release of the cells from the mica surface [55].

Recently, Panda and coworkers have developed a novel surfactant mediated fusion of polylactide particles into scaffold-like structures at room temperature, which enables the fabrication of the desired shape and size. In the presence of ethanol, evenly spread surfactant coated polylactide particles fused immediately into membrane-like structures. These scaffolds supported three-dimensional growth of animal cells *in vitro*. They were also found to be good wound dressing materials, as well as demonstrated to release a model protein in a sustained manner for a long period of time, making them suitable for various biomedical applications [56].

(4) Template for nano-fabrication

Recently, a surfactant-like AGD peptide, which could undergo self-assembly in nonpolar solvent system, was shown to bear a potential for the fabrication of nanostructures and nanodevices. This peptide was designed to have a shape like an inverted wedge which prevented it from self-assembling in an aqueous solution. However, in a nonpolar mixture of water and tetrahydrofuran, and in the presence of copper ions, the peptide could self-assemble into nanorings by forming reversed micelles [57]. Copper ions were shown to be bound to the negatively charged head of the peptide and embedded in the core of the nanoring. The peptide could thus be applied as a template for fabricating novel metallic nanostructures.

The self-assembly of surfactants has enabled the synthesis of ordered mesoporous silica nanoparticles with high surface area, diverse compositions, variable pore structures, and tunable pore sizes, which are promising materials for various applications, such as drug delivery, catalysis, and sensors [58, 59]. Kim and coworkers have developed a facile, one-step method for achieving systematic control of the surface properties of highly fluorescent graphene quantum dots (GQDs), thus giving them a surfactant-like property. The surface-modified GQDs could effectively stabilize oil-in-water Pickering emulsions and submicron-sized colloidal particles in mini-emulsion polymerization. These newly developed GQD surfactants were also employed in liquid–solid systems, for tailoring the dispersion of graphite in methanol. In addition, their luminescent property makes them potentially applicable as fluorescent sensors and for imaging [60].

2.2.3.7 Amyloid Nanofibrils

Another class of self-assembling peptides is the amyloid nanofibrils, which aggregate into β -sheet-rich supramolecular polymers. They have been reported to play a central role in the pathogenesis of various diseases ranging from neurodegenerative diseases (e.g., Alzheimer's disease and Parkinson's disease) [61] to type II diabetes [62] and cardiovascular diseases [63]. In addition to their pathological role, amyloid fibrils have recently been reported to serve as biocompatible and functional materials. For instance, amyloid fibrils deposited onto an inorganic surface can lead to the formation of a biological thin film that is suitable for bacterial growth [64, 65]. Amyloid fibrils can act as a catalytic scaffold [66] that enhances a biochemical reaction, and as a transporting or storing agent that contains or transmits genetic information [67, 68] and/or hormones [69]. Moreover, amyloid fibrils have recently been employed for developing biomimetic and functional materials whose properties can be controlled. For example, Li et al. developed a biomimetic composite material synthesized by coupling amyloid fibrils and graphene sheets and showed that the properties of such a composite material can be tuned by controlling elements of the chemical environment, such as humidity [70]. Moreover, Tuomas et al. have shown that a thin film made of amyloid protein fibrils was both biologically compatible and highly rigid, with a Young's modulus of up to 5–7 GPa, which is comparable to the highest values for proteinaceous materials found in nature [71].

Recent studies have reported that the mechanical properties of amyloid fibrils are determined by their molecular structures, such as steric zipper pattern or helical pattern, and by their length [72–75]. Furthermore, Lee et al. have recently shown that the structural characteristics (e.g., helical pitch, diameter, and length) of amyloid fibrils can be controlled using microwave-assisted chemistry. The microwave affects the thermodynamics of protein aggregation, which is responsible for the formation of amyloid fibrils [76]. This study may provide insight into the conformational heterogeneity of amyloid fibrils, not only for further understanding the origin of amyloid-driven pathogenesis, which is dependent on the conformational diversity of amyloid fibrils, but also for consolidating a design principle that is applicable for developing biocompatible and biomimetic materials [77].

2.2.4 Short Aromatic Peptides

A very interesting class of peptide nanostructures is based on the use of short aromatic peptides which form well-ordered nanostructures. The first peptide described in this group was diphenylalanine (FF), which is the core recognition motif of the β -amyloid polypeptide [78]. Through a systematic reductionist approach, FF was recognized as the smallest sequence to form peptide tubular nanostructures by self-assembly. These biocompatible and water soluble tubes are formed under mild conditions and are easy and inexpensive to manufacture [78]. Since its discovery, the

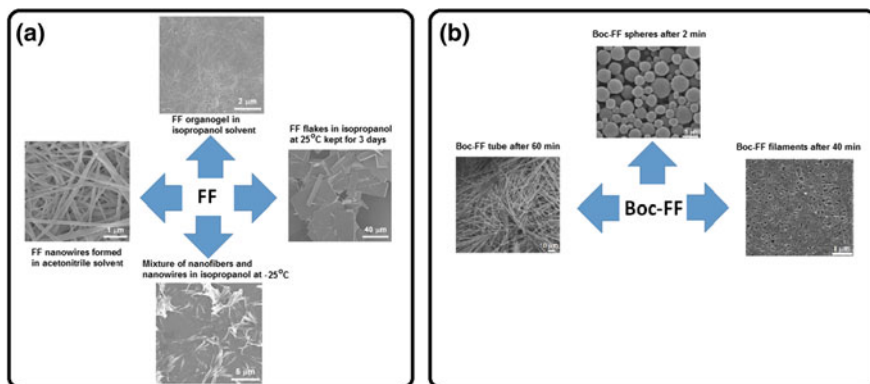


Fig. 2.2 Short aromatic peptide self-assembles into various morphological structures. **a** Diphenylalanine peptide (FF) self-assembles into nanowires in acetonitrile and into organogel, flakes nanofibers and nanowires in isopropanol (Reprinted with permission from Ref. [85] Copyright 2014 Royal society of chemistry. **b** Boc-FF peptide exhibits phase transition from spheres to filaments and finally into tubular structures (Reprinted with permission from Ref. [86] Copyright 2014 Macmillan Publishers Limited, part of Springer Nature)

FF motif has gained popularity as a minimalist building block to drive the self-assembly of short peptides and their analogues into different morphologies by subtle chemical changes introduced to the structure of the FF dipeptide or to the solvent [79, 80]. Various FF peptide derivatives were shown to self-assemble, forming ordered nanostructures, including tubes, spheres, plates, and hydrogels [81–84]. In addition, temperature-induced reversible self-assembly of the FF peptide and its structural transition from organogel to crystalline nanowires in acetonitrile and isopropanol solvent have been reported by Huang et al. [85] (Fig. 2.2a). Another interesting example is the protected dipeptide, tert-Butyloxycarbonyl-diphenylalanine (Boc-FF), which can associate into distinct morphologies at the nanoscale as a result of variations in the assembly conditions, such as solvent composition or peptide concentration [80]. Under certain conditions, the process of assembly can undergo several stages, and a clear phase transition is observed. Boc-FF first assembles into spheres, then forms filaments and finally transforms into tubular structures (Fig. 2.2b) [86].

2.2.4.1 The Short Aromatic Peptide Unique Physical Properties

The tubular structures formed by aromatic short peptides have been extensively studied over the past decade, and their unique properties were characterized. The FF nanotubes have been shown to be stable in the presence of organic solvents and to have extraordinary thermal stability properties [87, 88]. In addition, the FF peptide nanotubes (PNTs) exhibit a variety of physical and chemical functionalities, such as optical wave guidance [89, 90], luminescence [91], semi-conductivity [92], and

piezoelectricity [93, 94]. In addition, the FF nanotubes show remarkable mechanical rigidity, with direct atomic force microscopy (AFM) measurements indicating an average point stiffness of 160 Nm^{-1} and a calculated Young's modulus of about 20 GPa for nanotubular peptide assemblies [95]. A similar Young's modulus value ($27 \pm 4 \text{ GPa}$) was obtained in an independent study using a bending beam model [96]. Based on their mechanical properties, FF PNTs were utilized as nanofillers for composite materials with epoxy resin as the matrix. This resulted in an increase of about 70% in shear strength and a 450% increase in peel strength as compared to unmodified epoxy, while preserving the thermal and elongation properties similar to the original resin. These effects exceed the reinforcement effect of several known inorganic nanofillers, making FF PNTs excellent nanofillers for composite materials [97].

The mechanical properties of the spherical Boc-FF structures were also explored. A direct set of measurements, conducted using an AFM diamond-tip cantilever, demonstrated a remarkable Young's modulus of $\sim 275 \text{ GPa}$, an order of magnitude higher than the tubular FF assemblies [98]. The mechanical properties of the nanostructure can also be tuned using two peptides of differing stereochemistry: the L-form of the FF peptide and the D-form of the dinaphthylalanine peptide, which co-assemble to form nanotubular structures. Elevating the portion of the dinaphthylalanine peptide in the peptide mixture decreases the nanostructure's stiffness [99]. A density function theory (DFT) study was used to evaluate the basis for the mechanical rigidity of the nanotubes, suggesting that despite the porous nature of the crystal lattice, there is an array of rigid nanotube backbones with interpenetrating "zipper-like" aromatic interlocks that result in stiffness and robustness [100].

2.2.4.2 Low Molecular Weight Hydrogels

Chemical modification of short peptides by a variety of aromatic groups may aid in self-assembly via π - π stacking. For example, it has been shown that the addition of an aromatic group, such as carbobenzyloxy, naphthalene, or fluorenylmethoxycarbonyl (Fmoc), to the N-terminus of some peptides allows them to form stable hydrogels [101]. The short hydrogel-forming aromatic peptide systems are composed of four main components: a synthetic aromatic moiety coupled to the N-terminus of a short sequence peptide, typically a dipeptide or even a single amino acid [2], a linker between the peptide sequence and the N-terminal aromatic moiety which influences the structural orientation of the nanostructure [102], and a C-terminus which can be functionalized [103–105] and is also essential for the balance between protonated and ionized forms. Together, these four segments form a stable self-supporting system, which enables self-assembly of a short peptide sequence, whereas previous systems required a minimum of eight amino acids in each peptide chain [28]. This design is possible due to the combination of π - π stacking interactions and hydrogen bonding of the peptide portion [106].

Hydrogels are of great interest as a class of materials for tissue engineering and regeneration, since they offer 3D scaffolds to support the growth of cultured cells.

The short aromatic peptide-based hydrogels are self-supporting and display rheological behavior that is characteristic of solid like gel materials [101, 107, 108]. In particular, Fmoc-FF hydrogel can support cell growth, release of small molecules in a controllable manner, and exhibits remarkable physical properties. The Fmoc-FF hydrogel storage modulus G' was shown to be higher than 2×10^4 Pa, whereas other peptide hydrogels have a G' value of 50 Pa at a frequency of 1 Hz [108]. This study was later expanded by examining additional members of the aromatic dipeptide family, with a new set of Fmoc-peptides, which included both natural and non-natural aromatic amino acids. One product of the peptide building blocks assembly was a hydrogel that presented the cell-adhesive arginine–glycine–aspartate (RGD) motif as a bioactive ligand at the fiber surface and thus mimicked certain essential features of the extracellular matrix [83, 106]. The nanofibrous hydrogel presented by Zhou et al. is a mixture of two short aromatic peptide derivatives, Fmoc-FF and Fmoc-RGD. Cylindrical nanofibres interwoven within the hydrogel causes the presence of RGDs in tunable densities on the fiber surface [106]. These scaffolds may offer an economical approach for fabricating 3D-culture scaffolds with other bioactive ligands for in vitro tissue regeneration.

Moreover, QDs were incorporated into 3D fibrous organogel scaffold based on the FF peptide. To prepare the organogels, FF dipeptide is first dissolved in HFIP and the organic solvent is then added to enable gel formation. The gelation process can be observed exclusively in chloroform or in aromatic solvents, such as toluene or xylene. The FF gelation occurred in the presence of QD solution and the gels displayed photoluminescence from the embedded QDs. The emission maxima of the QDs in fibrous networks were slightly blue-shifted compared to those of free QDs, indicating the attachment of the QDs to the fibrils, but they maintained the

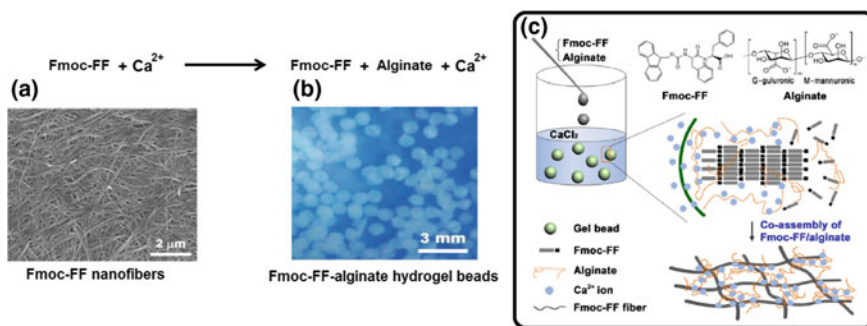


Fig. 2.3 Fmoc protected aromatic peptide self-assembles into various morphological structures in the presence of Ca^{2+} ions. **a** SEM images of Fmoc-FF nanofibers formed in the presence of Ca^{2+} ions. **b** SEM images of Fmoc-FF-alginate hydrogel beads formed in the presence of Ca^{2+} ions. **c** Schematic representation of Ca^{2+} ion-triggered co-assembly of peptide and alginate at an aqueous liquid–liquid interface to synthesize Fmoc-FF–alginate hydrogel beads (Reprinted with permission from Ref. [110] Copyright 2016 Royal society of chemistry)

original photoluminescence colors [109]. A new approach was reported by Xie et al. [110] who used calcium ions to trigger the self-assembly of the Fmoc-FF peptide into nanofibers with diameter of about 30 nm (Fig. 2.3a) while alginate was rapidly crosslinked by the calcium ions, thus forming stable hybrid hydrogel beads (Fig. 2.3b). Figure 2.3c shows a schematic representation of co-assembly of peptide and alginate at an aqueous liquid–liquid interface induced by calcium ions to synthesize Fmoc-FF–alginate hydrogel beads. They further used these hydrogel beads for drug delivery applications *in vitro*.

2.2.4.3 Applications of Short Aromatic Peptides

The minimal size and the simple synthesis of the short peptide building blocks, as well as the efficient and reproducible assembly procedures and unique physical properties, have attracted many research groups to develop various applications utilizing the aromatic dipeptide system. The short aromatic peptides are used in various applications ranging from biomedical applications, including nanomedicine, drug delivery, tissue engineering and biomaterials, to technological applications, including metal–organic frameworks applications, ultra-sensitive sensors, energy storage devices, and hydrophobic coatings [111–113].

Recently it was shown that self-assembled tetra-peptides which include the FF motif are substrates of cathepsin proteases, which are highly elevated in cancer and other pathologies. The degradation of one of these substrates by cathepsin led to the release of $91.8 \pm 0.3\%$ of the incorporated anti-cancerous drug Doxorubicin from the nanofibers within 8 h. Therefore, such peptides could serve as a platform for targeted drug delivery to pathologies in which protease activity is highly elevated [114]. Furthermore, Bonetti et al. showed that fluorinated β -peptides containing two aryl units can form nanotubes that are stable to protease degradation and to heating up to 120 °C and can locate in the perinuclear region of cells. Cytotoxicity assays were performed on cultured primary human smooth muscle cells, which are derived from human blood vessels, and thus offer a good model to represent the most abundant cell type directly exposed to nano-therapeutics present in the blood system. After 48 h, no cytotoxic effect was noted for peptide concentrations ranging from 1 to 100 μM , while at 200 μM cell viability was significantly reduced to approximately 80% relative to the control [115].

Another example is the growth of FF peptide microrods with fully controlled polarization and improved piezoelectricity for fabricating a power generator. The outputs of the FF peptide-based generators were shown to exceed other bio-inspired generators, and are even better than some inorganic generators. This study makes a significant step toward developing bio-inspired materials for piezoelectric devices to be used to generate renewable and biocompatible energy sources and for biomedical applications, and opens up a portal to the next generation of multi-functional electronics compatible with human tissue [116].

2.2.5 Coiled Coils

The coiled coil is one of the basic folding patterns found in native proteins, consisting of two or more α -helical peptides that are twisted around each other in super helical manner [2]. The primary structure of coiled coil forming proteins is characterized by a heptad repeat pattern $(\text{abcdefg})_n$, where n is the number of repeats. Positions a and d are occupied by hydrophobic amino acids that form the hydrophobic core of the coiled coil, which is characterized by a tight packing of the hydrophobic amino acid side chains in a “knobs-in-holes” fashion, while e and g are charged amino acid functional groups, which can interact to form stabilizing inter-strand salt bridges. The hydrophobic interaction between residues a and d and the electrostatic interaction between residues e and g contribute to the stability of the coiled coil structure [2, 117]. Expansion of the hydrophobic core to include the e and g positions and restriction of ionisable residues to positions b, c and f improved the oligomerization state and thermal stability of the coiled coil [118, 119]. In this stable arrangement, the side chains were positioned along the outside of the coil. The specificity and stability of coiled coils depend on the number of helical strands and the orientation of the helices and are affected by hydrophobic core packing and inter-helical ionic interactions [117].

The highly selective and specific binding properties of coiled coils and their easy manipulation using external stimuli, as well as the biological applications of many coiled coils, have stimulated the interest in the use of these fascinating motifs as building blocks for the development of novel bio(hybrid) materials. Coiled coil based bio(hybrid) materials have been recently used for various applications, including drug delivery, protein labeling, and bio-sensing [120].

Like other supramolecular building blocks, coiled coils can be used to construct a variety of distinct nanostructures of controlled size and shape in some selective solvents. For example, Holowka et al. reported the preparation of charged amphiphilic block copolypeptides that formed vesicles and micelles in water. These coiled coil nanovesicles composed of peptides with hydrophilic residues in one part and hydrophobic residues in another part, allowed encapsulation of dextran [121]. The stability and unfolding of coiled coil motifs depend on the temperature, pH, and ionic strength, which is often used in the design of controlled release delivery systems that respond to a specific stimulus [117]. Furthermore, the distinctive association-dissociation and spatial recognition of coiled coils make them ideal candidates for physical cross-linkers of protein-based supramolecular fibrils or polymer hydrogels [122, 123].

A number of examples of coiled coil α -helical fibrous structures have been presented by the Woolfson group [124–126]. Using a bottom-up design approach, they developed a two-component peptide system for making hydrogels, termed hSAFs (hydrogelating self-assembling fibers) [127]. These dual-peptide systems form gel only on mixing, which allows for tight control over assembly. They have a

wide variety of potential applications in biotechnology and medicine, such as the controlled delivery and release of cells, cosmetics and drugs, and as supports for cell growth and tissue engineering. The peptide sequences can be engineered to alter the underlying mechanism of gelation and, consequently, the hydrogel properties. Furthermore, the original two-peptide hSAF system can be supplemented with other components to endow cell-binding functions to the system, hence building up complexity and functionality [124].

Recently, Mondal et al. presented the first-ever self-assembling single heptad repeat module, based on the ability of the non-coded α -aminoisobutyric acid to stabilize very short peptides in helical conformation [128]. A conformationally constrained peptide comprised of aromatic, but not aliphatic, residues at the first and fourth positions formed helical fibrillar assemblies. New analogues of this motif can be accurately designed due to the high-resolution crystal structure of the helical assemblies. Substitution at different positions of the heptad sequence while maintaining the relative arrangements of hydrophobic amino acids and introduction of additional functionalities through side chain modifications can give rise to a vast repertoire of helical assemblies with possible applications in bionanotechnology and biomaterials.

2.3 Conclusions and Future Perspectives

SAPs have been gaining increasing attention as versatile structural building blocks with the ability to generate diverse supramolecular architectures with tunable functionalities. Since various functionalities can be incorporated into the peptide sequence, including self-assembly, cell attachment, or signaling domains, versatile, multifunctional structures can be generated from a single molecular entity. Along with their easy production, these advantages make SAPs attractive for various biomedical applications. However, extensive studies are still required addressing the rational peptide design to understand thoroughly the role of hydrophobicity, electrostatics, and size on pattern formation and to examine the fundamental physical interactions that drive their unique self-assembly. Particularly, for biological applications, a systematic structure–function understanding of self-assembled peptides are required to evaluate the properties of peptide nanostructures upon pH change, high protein and salt concentration, control of the size of peptide nanostructures for developing drug delivery systems and biosensors, as well as to develop nanostructures of equivalent dimension for the fabrication of bio-sensing platforms and determine an optimal balance of hydrophobicity and charge to minimize aggregation through hydrophobic groups. Also, the study of unexplored peptide sequences is required to develop the next generation of self-assembled peptides for various applications.

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