Self-Assembling Peptides: From Molecules to Nanobiomaterials

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Abstract | Molecular self-assembly plays a vital role in the construction of various nanostructures using the 'bottom-up' approach. Peptides have been considered important bio-molecular building blocks for different nanoscale structures as they are biocompatible, biodegradable, generally non-toxic and can be attuned to environmental responses like pH, temperature, salt concentration and others. Peptide based nanostructures can offer various wonderful biological applications in tissue engineering, cell culture, regenerative medicine and drug delivery. In this review, the construction of short peptide-based different nanostructures including nanotubes, nanovesicles and nanofibers, short peptide-based nanoporous materials, short peptide-based nanofibrous hydrogels and nanovesicles for various biological applications has been discussed. Moreover, morphological transformations from one nanoscopic structure to an other type of nanostructure (e.g., nanotubes to nanovesicles) are also clearly discussed in this review.

1. Introduction

Soft nanostructures are particularly important because they can be attuned to various environmental responses.[1,2] Biomolecular building blocks including peptides, lipids, nucleosides and others are interesting candidates which can be self-assembled under appropriate conditions to form different nanoscale structures.[1–5] Self-assembling peptides are one of the most attractive and useful building blocks in making various nanostructures including nanotubes, nanorods, nanovesicles, nanobelts, nanofibers and others due to their chemical diversity, biocompatibility, biodegradability and foldability into specific structures depending on the sequence and environmental responses. These peptide based building blocks can be self-assembled in water using various non-covalent interactions including hydrogen bonds, π-π stacking interactions, electrostatic interactions and hydrophobic interactions to form a specific type of nanostructure depending on suitable conditions. Stimuli-responsive nanostructures are of particular importance as these nanostructured biomaterials can be used as stimuli-responsive nanocarriers for delivering drugs and other important biological molecules to the target sites. For example, nanovesicles can be envisaged as nanocarriers for carrying drugs and other important biomolecules in response to environmental systems like pH, temperature and others.[6] Environmental response is very important in controling the self-assembly pattern of a specific building block and dictating the formation of a particular type of nanostructure under specific conditions. This is because pH, concentration of the peptide, and salt concentration can play an important role in nanostructural transformation. The self-assembling short peptide-based nanoporous materials can be considered a new class of nanoporous materials as they not only differ from the existing type of nanoporous

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materials like zeolites, metal organic framework (MOF) and others, but are also found to be biodegradable and eco-friendly materials.[7] We will focus, in this review, on self-assembling, water soluble short peptide(with two to seven residues) based various nanostructure formations, nanostructural transformations, short peptide-based nanoporous materials, short peptide-based nanofibrous hydrogels with their various applications, nanovesicles such as drug delivery vehicles and amyloid-like fibril formations.

Hydrogel: Hydrogel is an important type of soft material in which numerous water molecules are getting trapped within the network structure given by the gelator molecules under appropriate conditions.

Amyloid: Amyloids are fibrous protein aggregates, insoluble in nature and they share specific structural features. Unusual deposition of amyloid in organs leads to amyloidosis and can play a key role in many neurodegenerative disorders.

2. Short Peptide-Based Nanobiomaterials

Various nanostructures including nanotubes, nanovesicles, nanorods, nanofibrills, nanobelts and others have been obtained from self-assembling short peptide-based building blocks. Among these nanostructures, peptide-based nanotubes and nanofibrils are very common and can offer various applications in biology.

3. Tubular Peptide Nanostructures

Cyclic peptide-based nanostructures can be regarded as the first engineered structures. Ghadiri and his coworkers have made a pioneering contribution in the construction of cyclic peptide-based nanotubes.[8–10] They conceptualized the self-assembly of alternating D- and L-α-amino acid-based cyclic peptides through intermolecular hydrogen bonding to form nanotubular structures with a desired diameter. The diameter of the nanotube can be varied depending on the ring size of the cyclic peptide building blocks. Different amino acid residues including unnatural amino acid residues can be incorporated into the cyclic peptide building blocks as the side chain of the amino acid residue can be manipulated. Granja and his co-workers have used a different self-assembling building block based on a hybrid of α-γ-cyclic peptides in making peptide nanotubes.[11,12] These nanotubes have various applications as antibacterial agents, artificial photosystems, biosensors, catalysts and others.[13–19] There is a recent review regarding cyclic peptide nanotubes by Granja and his co-workers.[20]

Relatively less attention has been paid to linear peptide-based nanotubes. Görbitz and his co-workers made a seminal contribution in the field of short peptide-based nanotubes. Linear water-soluble hydrophobic dipeptides (L-Leu-L-Leu, L-Leu-L-Phe, L-Phe-L-Leu, and L-Ile-L-Leu) can be self-assembled utilizing head to-tail ($NH_3^+ \cdots {}^-OOC$) hydrogen bonds to form nanotubular structures.[21–25] These nanotubular structures contain water molecules inside the core channel.[21–25] Another example of water-filled nanotubes is a dipeptide (tryptophylglycine) and these nanotubes show negative thermal expansion.[26,27]

The self-association of the Phe-Phe dipeptide is really interesting as this sequence is the core recognition element found in the β-amyloid polypeptide.[28] Nanotubes are formed from the self-assembly of this dipeptide in water[29] and also in crystals.[30] These nanotubes are thermally and chemically stable.[31] Vapour deposition methods at 200° C using a vacuum chamber have been used by Gazit and his coworkers to prepare self-assembled large arrays of short aromatic peptide-based nanotubes.[32] They have also demonstrated that arrays of aromatic dipeptide-based nanotubes can find potential applications in developing high-surface-area electrodes for storing energies and making microfluidic chips.[32]

Chauhan and his coworkers have investigated the self-assembly process of a dipeptide containing a noncoded, achiral, α,β-dehydrophenylalanine residue (ΔPhe).[33] Introducing the ΔPhe residue in the peptide sequence makes it conformationally rigid, and also enables the peptide to resist proteolytic degradation. Interestingly, the dipeptide (Phe–ΔPhe) has been self-assembled into a distinct nanotubular structure. The thermostable, enzymatically stable and pH stable nature of this nanotube makes it useful for applications in biological systems and also in material science.

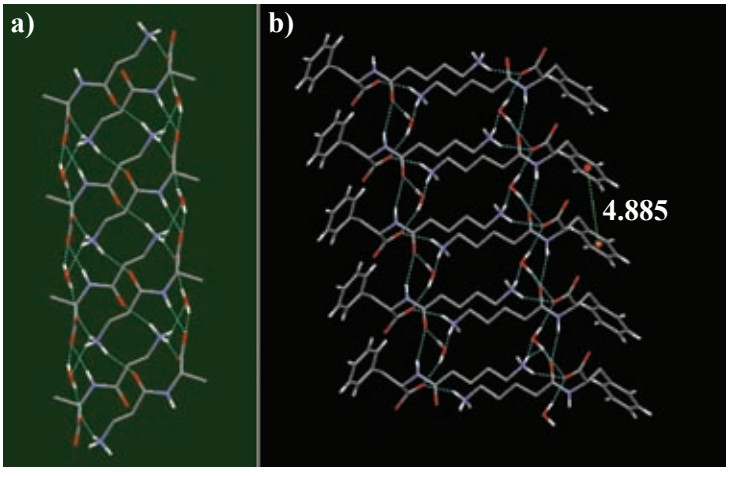
Zhang and his coworkers have contributed significantly in making peptide surfactant based nanotubes.[34–36] These peptide surfactants are composed of a hydrophilic head with one or two charged amino acid residues and a hydrophobic tail of four or more consecutive hydrophobic residues. Upon self-assembly in water, these peptides form open-ended nanotubes with diameters ranging from 30–50 nm.

Each of the two dipeptides (H_3 N^+-β-Ala(1)-Ala(2)-COO^- Peptide **1**; H_3 N^+-δ-Ava(1)-Phe(2)-COO^- Peptide **2**) containing an N-terminally positioned ω-amino acid residue (β-alanine/δ-amino valeric acid) self-associates to form nanotubes in the solid state as well as in an aqueous solution.[37] Though they form hollow nanotubular structures both in the solid state and in a solution, their self-assembling nature in these two states is different. This causes a difference in the internal diameters of these nanotubes in a solution and in a solid state structure. These nanotubes are stable proteolytically, thermally, and over a wide range of pH values (1–13).[37] In the crystal state, both peptides adopt an extended backbone conformation. A vital role has been played by water molecules in the formation and stabilization of nanotubular structures through intermolecular

hydrogen bonding along the crystallographic b axis (Figure 1).[37] Head to tail $NH_3^+ \cdots {}^-OOC$, $NH_3^+ \cdots O(W)$, $H(W) \cdots {}^-OOC$, $NH_3^+ \cdots O=C$ (amide), and amide $NH \cdots {}^-OOC$ intermolecular hydrogen bonds have been observed in the case of peptide **1**, in the formation of nanotubular architecture. Head to tail $NH_3^+ \cdots {}^-OOC$, $NH_3^+ \cdots O(W)$, $H(W) \cdots {}^-OOC$, $H(W) \cdots O=C$ (amide), and amide $NH \cdots O=C$ (amide) intermolecular hydrogen bonds have been observed in the formation of nanotubular architecture in the solid state in the case of peptide **2**.[37] Aromatic π-π stacking interactions with an average π-π distance of 4.9 Å are also responsible for the stabilization of nanotubular structures for peptide **2**. The temperature-dependent X-ray powder diffraction (XRPD) data clearly show that nanotubular structures are stable upto 70° C as the diffraction intensity and pattern remain unaltered for peptides **1** and **2** upto this temperature.[37] The TEM images of these two dipeptides reveal a uniform and well-ordered hollow nanotubular structures with a total diameter of 27 nm and an inner diameter of 5 nm for the peptide 1 nanotube, and a total diameter of 44 nm with a 15 nm inner diameter for the peptide 2 nanotube.[37] These peptide nanotubes are stable towards proteolytic degradation for more than 24 hrs as they are composed of N-terminally located proteolytically stable non-protein ω-amino acid residues in the peptide backbone. Solution state FTIR data and the crystal structure support the formation of intermolecularly hydrogen-bonded self-assembled β-sheet conformations for both peptides in solution and crystals. The folding of the extended β-sheet conformation along one axis of the 2D layered structure utilizing intermolecular hydrogen bonds and/or π-π interactions leads to the formation of a tubular structure in nanoscale.[37]

Three water-soluble short peptides each having a common motif, a hybrid of β,α-amino acid residues (β-Ala-L-Xaa, Xaa = Val/Ile/Phe) are self-assembled to form hollow nanotubes.[38] These nanotubes are stable towards heat up to 80° C, a wide range of pH (2–10), and against proteolytic degradation.[38] These dipeptide-based robust crystalline nanotubes have been used as suitable templates for fabricating dipeptide-stabilized gold nanoparticles on their outer surfaces.

Figure 1(a, b): Construction of water-mediated nanotubular structures using hydrogen-bonds obtained from self-assembling dipeptides **1** and **2** in crystals.[37]



4. Peptide Nanofibers

Peptide-based nanofibers as biomaterials have been extensively covered and reviewed elsewhere by different research groups.[39–41] We have, therefore, concisely discussed self-assembling short peptide-based nanofibers in this review. These nanofibers are very common and are biologically important materials with different applications.[2,42]

5. Amyloid Fibers

Amyloid fibrils are thought to be associated with a large number of fatal human diseases including Alzheimer's, Parkinson's, Type II diabetes and others.[43,44] Currently, there are about 20 human diseases which are linked to the formation of amyloid fibrils having diameters of 7–10 nm. These fibrils exhibit well-ordered structures. This indicates that they form a typical β-sheet conformation on self-association. Moreover, these fibers show a typical green- gold birefringence under polarized light after being stained with a water-soluble dye Congo Red. These fibers interact with another physiological dye Thioflavin T, and after binding with this dye these fibrils exhibit an emission at 482 nm. Amyloid fibrils are generally formed by polypeptides containing 30–40 amino acid residues. In this review, amyloid fibrils formed by self-assembling oligopeptides with less than eight amino acid residues will be discussed.

Kapurniotu and his coworkers have reported that a hexapeptide fragment of human IAPP forms a β-sheet forming typical amyloid fibrils upon self-assembly.[45] This hexapeptide exhibits structural and biophysical properties similar to that of a full-length 37 amino acid polypeptide. They have also shown that the short peptide and the full-length IAPP assemblies have the same cytotoxic activity towards the pancreatic cell line RIN5fm.[45] Serranno and his co-workers studied a series of de novo designed hexapeptides which

form amyloid fibrils upon self-aggregation in water. They have also shown the residue-specific propensity of amyloid fibril formation in a series of model hexapeptides.[46] Gazit and his co-workers have systematically investigated several tetrapeptide and pentapeptide fragments of the human calcitonin hormone, which forms amyloid fibrils.[47,48] They have also established the fact that aromatic-aromatic interactions play a vital role in amyloid fibril formation using model oligopeptides.[49] Johansson and his coworkers have shown that charged attractions and the β-sheet forming tendency are important criteria for the formation of amyloid fibrils from model tetrapeptides.[50]

Our group is also involved in studying synthetic self-assembling water-soluble tripeptides which form intermolecularly hydrogen-bonded supramolecular β-sheet structures and amyloid fibrils. A tripeptide Val–Ile–Ala, which has a sequence identity with the C-terminal section of the Alzheimer's Aβ-peptide (Aβ40–42), self-associates in crystals to form first a β-sheet structure, which, upon further self-assembly, gives rise to straight, unbranched nanofibrils showing amyloid-like behavior.[51] It is important to mention that the tripeptide Ala–Val–Ile has a different amino acid sequence. Though the composition of the amino acid is the same as that of the first one, it is unable to form amyloid-like fibrils. This suggests that the sequence-specific nature of a peptide is sometimes responsible in amyloid-like fibril formation.[51]

Another example of tripeptide-based amyloid nanofiber formation that was carried out by our research group includes the self-association of a hydrophilic tripeptide Gly-Tyr-Glu with a sequence identity of the N-terminal portion of an amyloid peptide Aβ(9–11). Upon self-assembly it forms amyloid-like fibrils.[52] These fibrils exhibit significant neurotoxicity against the Neuro2 A cell lines. However, the other two synthetic tripeptides Gly-Phe-Glu, Gly-Trp-Glu, in which the Tyr residue at the middle position has been substituted by Phe or Trp, do not exhibit any amyloidogenic behavior and show little or no neurotoxicity.[52]

Eisenberg and his coworkers have studied the microcrystals obtained from the fibril-forming oligopeptide segments of a prion protein Sup35 from yeast and the X-ray microcrystallographic study reveals the formation of cross-β spine structures at atomic resolution.[53] They have also reported the crystal structure of 13 other segments obtained from amyloid-like fibril-forming different proteins including segments from Alzheimer's amyloid-β and tau proteins, the PrP prion protein, insulin, islet amyloid polypeptide (IAPP), lysozyme, myoglobin, α-synuclein and β_2-microglobulin. This study indicates that all these segments obtained from different amyloid fibril-forming peptides share a common structural feature (cross-β spine structure) at the molecular level.

Nuttall and his coworkers have studied a crystal structure of the amyloidogenic segment of the Aβ peptide (spanning the residues 18–41) with a single variable domain antibody Ig new antigen receptor (IgNAR).[54] Their structural study correlates with the observable feature of non-fibrillar, small Aβ oligomers. This study also provides a model system for the formation of non-fibrillar oligomers in Alzheimer's disease.

Jelinek and his coworkers studied the self-aggregation property of a native penta-peptide fragment derived from the amyloidogenic human calcitonin sequence.[55] They have demonstrated that substitutions within the sequence of native penta-peptide can remarkably regulate the kinetics of peptide self-association, and the charge of β-sheet organization as well as modify fibrillar morphology.[55] Their results have also revealed that hydrophobic or aromatic-aromatic interactions are not absolutely necessary for the formation of peptide fibers.

Nilsson and his coworkers have demonstrated the role of hydrophobic, charge and steric effects on the self-association of a fragment of the amyloid Aβ peptide. Their study suggests that the amyloid fibril-forming potential depends on the collective influence of aromatic, hydrophobic and steric factors.[56] In another study, they have shown that the self-aggregation behaviour of the amyloid fragments of Aβ peptides is influenced by a secondary structure-forming propensity, hydrophobicity, charge of the amino acid residue and steric factors.[57]

6. Short Peptide-Based Nanofibrous Gels and Applications

Many peptide-based molecules do self-assemble in water to form supramolecular hydrogels. At the microscopic level, the morphologies of these supramolecular gels have been investigated by using conventional imaging techniques including SEM, TEM, and AFM. It has been found that most of these gels have a nanofibrillar network structure.[58–61]

In this review, we mainly discuss the short self-assembling water-soluble peptides, which can form supramolecular hydrogels under appropriate conditions.[58–68]

Ventura and his co-workers have reported that a dipeptide, Ile–Phe, can form hydrogel at 1.5 wt% at pH 5.8.[62] They showed that the gel is

transparent, and thermoreversible and forms a network of fibrillar nanostructures that exhibit strong birefringence upon Congo red binding.[62] The self-assembly of an α,β-dehydrophenylalanine residue (ΔPhe) containing dipeptide H-Phe-ΔPhe-OH, forms a hydrogel at a concentration as low as 0.2 wt% in a buffer solution.[63] The authors have investigated the ultrastructure of the gel using TEM and it was observed that the gel matrix is composed of a highly dense network of nanofibers, each of which is 15–20 nm in diameter and has a length in micrometers.[63] The gel matrix has been in use for the encapsulation and sustained release of several bioactive molecules including vitamins like ascorbic acid, riboflavin, and vitamin B_{12}, antibiotics like ampicillin, and antituberculosis drugs like L-cycloserine and isoniazid. This hydrogel does not exhibit any observable cytotoxicity towards the HeLa and L929 cell lines.

Chauhan and his coworkers have reported the 3D growth of mammalian cells (HeLa and L929) on a chemically functionalized dipeptide-based hydrogel system.[64] The dipeptide (Phe-ΔPhe) based hydrogel has been functionalized with an "RGD" containing pentapeptide to facilitate the growth of cells and their proliferation. This functionalized hydrogel provided a wonderful support for 3D cell growth for more than two weeks and showed the viability of the cells, their spread and growth. This study provides an excellent example of a simple peptide based-hydrogel to attain increased cell growth, and promoting properties, with its high enzymatic stability. This gel-based soft material acts as a convenient template for 3D cell growth with a probable use in tissue engineering and cell biology.

The self-assembly of a pentapeptide fragment of the amyloid β-peptide NH_2-KLVFF-COOH has produced a hydrogel in a phosphate-buffered saline (PBS) solution.[65] It is expected that the screening of the electrostatic charges of the gel-forming peptide enables β-sheets to self-associate to form a nanofibrillar gel network.[65]

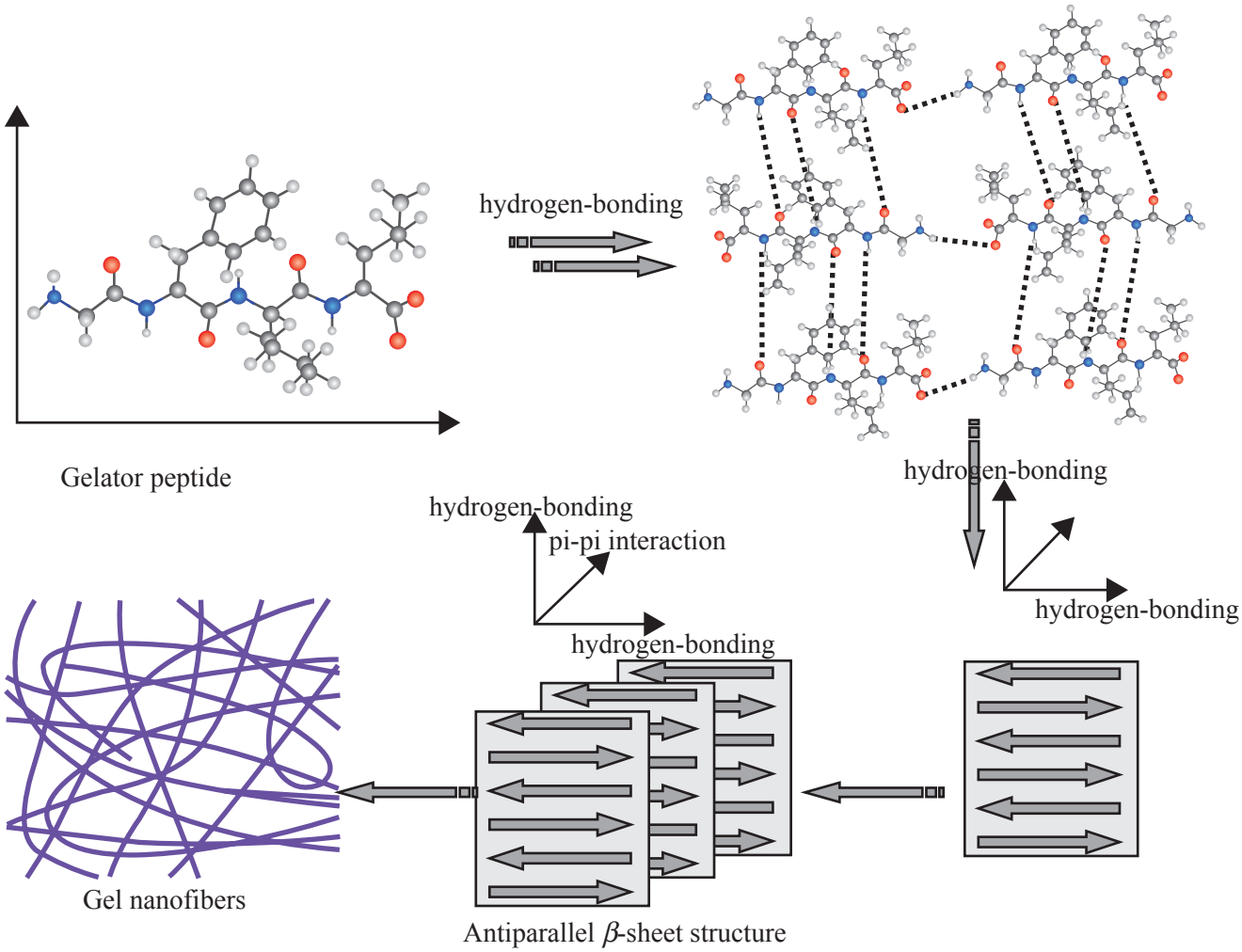
Two self-assembled oligopeptides, namely, H_2 N-Gly-Ala-Ile-Leu-COOH (peptide **3**) and H_2 N-Gly-Phe-Ile-Leu-COOH (peptide **4**), can form hydrogels at physiological pH.[66] These hydrogels are pH-responsive and thermoreversible. Different microscopy, including field emission scanning electron microscopy (FE-SEM), transmission electron microscopy (TEM), and atomic force microscopy (AFM) clearly reveal the presence of a long interconnected nanofibrillar network structure in the gel phase.[66] Fourier transform infrared spectroscopy, circular dichroism and wide angle X-ray diffraction studies support an antiparallel β-sheet conformation of these gelator peptides in the gel phase. From these observations, a tentative model (Figure 2) has been proposed representing the formation of the gel fibers from the gelator peptide **4**.[66] The authors have used these hydrogels for the entrapment and slow release of an anticancer drug doxorubicin at physiological pH, promising their future applications as drug delivery vehicles.[66] These hydrogels can entrap 8.62×10^{-3} (M) and 13.79×10^{-3} (M) drug solutions (for hydrogels obtained from peptide 3 and 4 respectively) at their respective minimum gelation concentrations. It has observed from the drug release curve that almost 85% (for the gel of peptide 3) and 90% (for the gel of peptide 4) of the drug molecules have been diffused from the respective gel matrix after 45 h. The authors have also calculated the diffusion coefficients from the release curve and these are 2.078×10^{-10} m^2 s^{-1} for the hydrogel obtained from peptide **3** and 2.737×10^{-10} m^2 s^{-1} for the hydrogel obtained from peptide **4**.

Adams and his co-workers have reported the formation of nanofibrillar network structures obtained from self-assembling α-helical linear peptide-based gels.[69] There are several examples of aromatic residue-containing short peptide-based hydrogels and these gels provide nanofibrillar network structures upon electron microscopic examination. Peptides with various hydrophobic conjugates including aromatic moieties like fluorenylmethoxycarbonyl (Fmoc),[70–81] naphthalene,[82–88] and pyrene[89,90] can provide good opportunities to be assembled in water using the π-π stacking interaction and hydrophobic interaction to form a nanofibrillar hydrogel network.

Xu and his coworkers have reported enzymatic intracellular hydro-gelation inside a bacterium (E. coli).[91] An enzyme (phosphatase) was over-expressed in E. coli and this was observed to trigger the formation of a hydrogelator within the bacterium (Figure 3). This hydrogelation inside the cell was found to inhibit the growth of the bacterium.[91] This strategy, enzyme-assisted intracellular self-association of peptided-based molecules for making artificial nanostructures and thus regulating the fortunes of cells can give rise to a new method to manage the cellular process, comprehend cellular function and develop new therapeutic agents at the supramolecular level.

Bing Xu and his coworkers have demonstrated that tripeptide derivatives conjugated with olsalazine (a clinically used anti-inflammatory prodrug) exhibit excellent self-assembling properties in water to form prodrug-containing supramolecular hydrogels.[92] They have also shown that the reduction of the azo group can disrupt the supramolecular

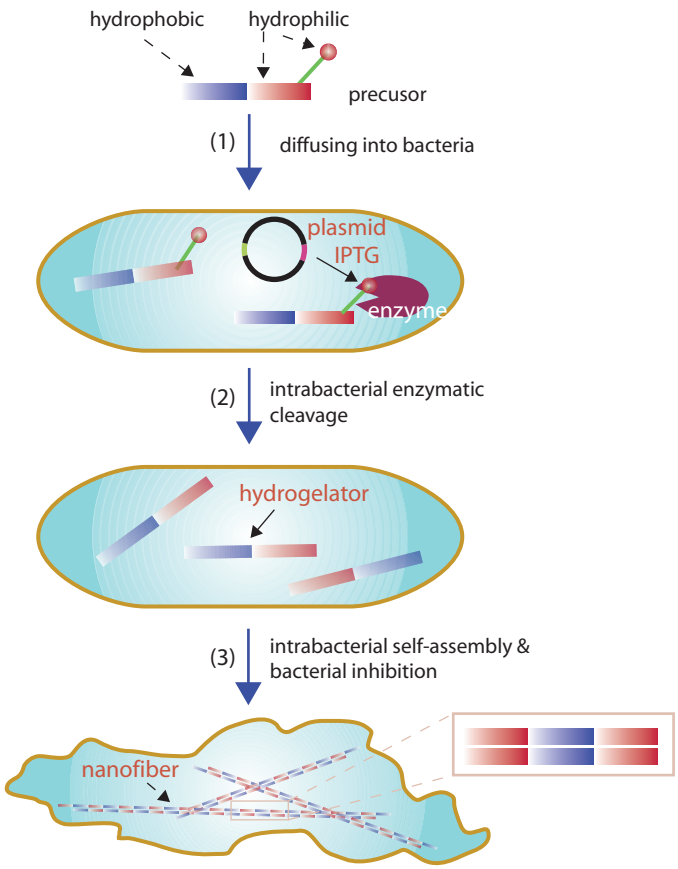
Figure 2: A tentative model representing the molecular arrangement of the self-associating peptide **4** in the gel phase.[66]



hydrogels and this results in the controlled release of an anti-inflammatory agent 5-aminosalicylic acid. This method may be useful for developing new nanobiomaterials to develop drugs at specific sites.

Self-assembling peptides and peptide derivatives that form nanofibrillar gels have attracted considerable interest as extracellular matrices for various applications in 3D cell culture, tissue engineering and regenerative medicine. There are several examples of nanofibrous hydrogels as an extracellular matrix for the growth of cells. Ulijn and his coworkers have reported a peptide-based bioactive hydrogel using the molecular self-assembly of a mixture of two aromatic short peptide derivatives: Fmoc-FF (Fluorenylmethoxycarbonyl-diphenylalanine) and Fmoc-RGD (arginine-glycine-aspartate).[93] This biomimetic nanofibrous hydrogel acts as a 3D-scaffold for anchorage-dependent cells. Yang and his coworkers have developed a hydrogel from a collagen mimic peptide sequence.[94] They have shown that this hydrogel has been considered a promising and interesting biomaterial to maintain and to differentiate embryonic stem (ES) cells. This study holds the future promise of using stem cells containing molecular hydrogel in regenerative medicine. In another study, it has been found that hydrogels can be obtained from the N-terminally protected peptide sequence Nap-FFGRGD.[95] This hydrogel has been used for surface coating to functionalize poly(3-caprolactone) (PCL) films, and to promote cell attachment and growth. The potential applications of nanofibrillar peptide gels for biomedical uses have also been reported. Fibril-forming peptide gels were combined with cardiomyocytes or non-differentiated stem cells and this mixture was injected into damaged heart tissues for the improvement of transplanted cell survival and wound healing after a myocardial infarction.[96,97]

Figure 3: A schematic representation of intracellular nanofiber formation leading to hydrogelation and the inhibition of bacterial growth. Adapted with permission from ref 91. Copyright 2007 Wiley-VCH.



However, caution should be exercised in employing these nanofibrillar biomaterials for *in vivo* applications. This is because of some factors that can impact their immunogenecity and the interaction of these fibrils with inflammatory cells. There are a few reports on the examination of the immunogenecity of peptide-based fibrillar hydrogels. [98–101]

7. Peptide Amphiphile Based Nanofibers

Interestingly, β-sheet-forming peptides have an extraordinary ability to form one-dimensional nanostructures using intermolecular hydrogen bonding. Further, interactions among the one dimensional nanostructures obtained from these peptides give rise to the production of a three-dimensional network structure. Stupp and his coworkers have developed a broad range of synthetic peptide-based amphiphilic molecules, which upon self-assembly form nanofibers.[102–106] These peptide-amphiphiles have a short hydrophobic segment, in most cases, an alkyl chain, attached to the N or C-terminus of an oligopeptide sequence with one or more hydrophilic residues. These peptide-amphiphiles generally self-assemble to form high-aspect-ratio nanofibers under specific solution conditions such as a particular pH, ionic strength of the medium and temperature.

Amphiphile: Amphiphile is a chemical compound containing both hydrophilic (polar, water-loving) and hydropobic (nonpolar, water-hating) properties.

Stupp and his coworkers also demonstrated that magnetic resonance (MR) agent conjugated peptide amphiphile based nanofibers can be imaged by the MRI technique, a very powerful diagnostic tool in clinical radiology, which provides three-dimensional structures of live tissues.[107]

The peptide-amphiphile (PA) modified scaffold has been used to increase the attachment of primary human bladder cells, and this study shows the potential biological application of PAs for the functionalization of polymeric materials conventionally used for tissue engineering to augment their bioactivity.[108] Another wonderful application of PA-based nanofibers includes the adhesion of neural cells, and the migration and outgrowth of neurites *in vitro*.[109] Moreover, these PA-based nanofibers exhibited extremely promising results in an animal model based on a spinal cord injury model of a mouse.[110] All these results encourage the use of these peptide-based biomaterials in regenerative medicine.[2]

8. Peptide-Based Nanoporous Materials

Solely inorganic materials like zeolites and metal–organic frameworks consisting of both organic and inorganic counterparts have been extensively examined due to the various applications of these porous materials in gas storage, molecular separation, chiral recognition, catalysis, ion exchange,andinsensors.[111–115]However,shortpeptide-based porous materials are a new entry in this family of nanoporous materials. Peptide-based nanoporous materials possess an interesting type of biomaterial. Görbitz has seminal contributions in short peptide-based nanoporous structures. Görbitz's dipeptides, Val-Ala and Phe-Phe class structures formed from hydrophobic dipeptides,[22–24,116–118] and Ripmeester's dipeptide-based porous materials can adsorb inert gases, such as Xe.[119–122]

The removal of poisonous gases and energy demands are important issues in today's world. Therefore, the absorption of poisonous gases including carbondioxide, and methane using porous materials are beneficial to the environment. Recently, Sozzani and his co-workers have demonstrated that each of the four crystalline dipeptides namely, Ala-Val, Val-Ala, Ile-Val and Val-Ile self-assemble to form nanoporous materials.[123] They have examined their adsorption, separation, and storage of various gases such as methane, carbon dioxide, and hydrogen.[123]

Recently, dipeptide-based nanoporous materials have also been reported by our research group.[7] A new type of dipeptide-based nanoporous material has been obtained from two water-soluble synthetic dipeptides namely β-alanyl-L-phenylglycine (peptide **5**) and L-phenylglycyl-β-alanine (peptide **6**). N_2 gas adsorption and desorption studies have been performed using these peptide-based nanoporous materials. The adsorption capacity has been found to be of 173 ccg^{-1} and 71 ccg^{-1} and BET surface area of 56.76 $m^2\ g^{-1}$ and 41.73 $m^2\ g^{-1}$ for these two peptides, respectively. Görbitz's porous materials obtained from hydrophobic dipeptides are based fully on α-amino acids and they have pore diameters ranging from 3–10 Å.[22,23,116] However, our reported dipeptide-based porous materials are composed of a hybrid of *a* and β-amino acids, with different pore sizes.[7] These pore sizes vary from 6.4 to 3.2 Å. Interestingly, these nanoporous materials obtained from dipeptides have been observed to be biodegradable towards the soil bacterial consortium. This suggests that these short peptide based nanoporous materials are eco-friendly. An example of porous materials based on cyclic peptide building blocks has also been reported by our research group.[124]

9. Peptide-Based Vesicles and their Applications

Vesicles seem to be enclosed spherical structures having the capacity to encapsulate various materials. The entrapped materials can be released by rupturing these vesicles under suitable conditions. Vesicles offer interesting functions including chemical-sensing/bio-sensing, encapsulation and sustained release of drugs and other biologically important molecules.[125] A report of Gazit and his coworkers includes diphenylglycine and diphenylalanine-based hollow nanospheres which exhibit significant stability.[126] Nanovesicles can also be obtained from self-assembling dipeptides α,β-dihydrophenylalanine residues (ΔPhe).[127] These vesicles can encapsulate small drug molecules and other biologically important molecules such as riboflavin, vitamin B_{12}, bioactive peptides and even a protein. These vesicles are resistant towards the proteolytic enzyme, proteinase K.[127]

A very recent report by our research group includes the development of nontoxic multivesicular structures from self-assembling water-soluble dipeptides containing glutamic acid residues at the C terminus.[125] These vesicles are stable over a wide range of pH (pH 2–12). However, these vesicles are responsive towards calcium ions. Interestingly, the encapsulation of the anticancer drug doxorubicin and its release in the presence of calcium ions has been observed. Furthermore, these vesicles can be used as carriers for biologically important molecules, such as cyclic adenosine monophosphate (cAMP) within the cells, while their biological functions remains unchanged. So, these peptide vesicles may be used as biocompatible drug delivery vehicles.[125]

10. Morphological Nanostructural Transformations

The transformation of one nanoscopic species to an other nanoscopic species is an interesting phenomenon. This transition from one nanostructure to another type of nanostructure e.g., nanotubes to nanovesicles can be either stimuli responsive or due to a slight change in the molecular structure. Precise control over the morphology of the nanostructure is a challenging task. Some molecular building blocks, upon self-assembly in a particular condition, can give rise to a particular nanoscale structure. The pattern or mode of assembly can be manipulated by the proper selection of pH, solute concentration, salt concentration or even by changing the solvent system.

A dipeptide (D-Phe-D-Phe) has been self-assembled in water to form a nanotubular structure with diameters ranging from 2 nm to 100 mm. Interestingly, vesicles have been observed in addition to the nanotubes, when this nanotube solution was diluted with an appropriate volume of water. This observation suggests that the concentration of the peptide plays a key role in determining the construction either of nanotubes only or of a mixture of nanotubes and nanovesicles.[128] An example of nanotube to nanovesicle conversion has been recently reported by Junbai Li and his co-workers. They have demonstrated that a cationic dipeptide (H-Phe-Phe-$NH_2 \cdot$ HCl) derived from Phe-Phe can be self-assembled into nanotubes at physiological pH. A spontaneous conversion from nanotubes to spherical vesicle-like structures occurs and it has been observed with the dilution of the peptide scaffold.[129,130]

Another fascinating example of nanovesicle to nanotube transformation observed by our research group includes the concentration dependent transformation of nanovesicles to nanotubes of an oligopeptide, Acp-Tyr-Glu (Acp, ε-amino caproic acid) at neutral pH.[6] This peptide self-assembles to form nanovesicles at a concentration of 6.9 $mgmL^{-1}$, whereas nanotubular structures have been observed at a concentration of 2.3 $mgmL^{-1}$. An ordered array of fused vesicular structures was formed at an intermediate concentration of 3.4 $mgmL^{-1}$ and this type of fused vesicular structure promotes the formation of a nanotubular structure upon dilution. In this study, the concentration of the peptide plays a vital role in dictating what type of nanostructure

can be formed: nanovesicles or nanotubes or fused vesicular structures (Figure 4). CD and FTIR data of the tripeptide Acp-Tyr-Glu suggest that the peptide adopts a turn-like structure in solution at neutral pH and this turn like structure is independent of dilution. A curved self-assembled structure can be formed from the self-association of the turn-like structure. A vesicular structure can be obtained by the two-dimensional layer closure of this curved supramolecular structure. The rolling up of this curved structure in one direction leads to the formation of a nanotubular structure (Figure 5). These vesicular structures are responsive towards biocompatible Ca^{2+} ions and pH of the solution.[6] The presence of calcium ions or high pH (10.7) triggers the breaking of these nanovesicles. These nanovesicles can entrap a potent anticancer drug doxorubicin and the drug can also be released in the presence of calcium ions. This holds out the promise of applying these nanovesicles as nanovehicles to carry drug and other biologically important molecules.

A report by our research group includes the pH-responsive nanostructural transition of a self-assembling tripeptide Tyr-Aib-Ala (Aib: α-amino isobutyric acid) from nanotubes to nanovesicles.[131] At acidic pH, a hollow tubular structure at nanoscale measurements has been observed. However, the uniform coexistence of both nanotubes and nanovesicles has been observed at pH 6.5. A further increase in pH leads to the formation of only one nanoscopic structure (nanovesicle) exclusively and these vesicles are stable in the pH range 7.0–9.2. The rupturing of these nanovesicles has been observed at a higher pH (pH >9.2). The entrapment and sustained release of a physiological dye, Congo red, has been performed using the pH-sensitivity of these nanovesicles.[131]

An interesting example of peptide–dendron hybrid-based nanostructural tranformation from nanotubes to nanofibrillar aggregates has been reported by Parquette and his coworkers. This transformation can be carried out either by changing the pH or altering the salt concentration (NaCl).[132] Only nanotubular structures have been observed at a lower pH (pH 1) and at a higher pH (pH 11) since, as the lysine side chains are deprotonated, a nanofibrillar structure is obtained. At lower salt concentrations (50 mM NaCl) a mixture of nanotubes and nanofibrillar structures have been found, while at higher concentrations of salt (100–200 mM), only nanofibrils have been obtained.[132]

The pH-triggered change in the morphology of a surfactant-like octapeptide, Ac-IIEENNDD-OH has been observed in aqueous solution. Twisted ribbons have been found at a pH less than 4. However, nanospheres have been obtained above pH 4.[133] Another example of pH-dependent nanostructural transformation includes the transition in a tryptophanezipper-formingpeptide-basedmolecule, from nanospheres to a mixture of nanospheres and nanofibers.[134] A solvent-dependent morphological transformation from a hollow nanosphere to a

Figure 4: A pictorial representation of the concentration dependent nanostructural transition from nanovesicles to nanotubes via an intermediate nanostructure, an ordered array of fused nanovesicles: (i) nanovesicles, (ii) an intermediate, well-defined array of fused nanovesicles, (iii) a nanotube.[6]

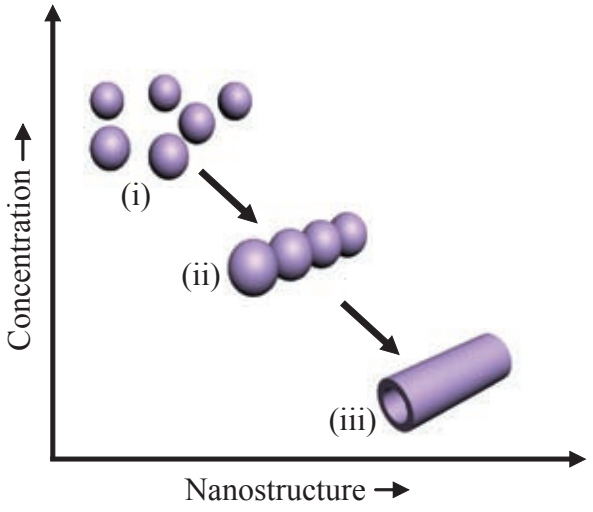
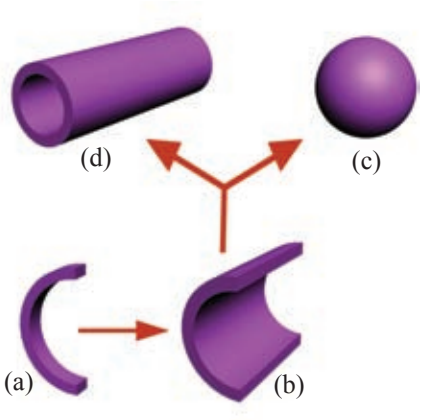


Figure 5: A tentative model for the formation of a nanotube and a nanovesicle from (a) turn-shaped molecular conformation, (b) molecular assembly with a curvature, (c) two dimensional layer closure of this curved structure gives rise to a nanovesicle, (d) rolling of this curved structure in one direction leads to the formation a nanotube.[6]



nanofiber in a peptide based soft self-assembly has been reported by Verma and his coworkers.[135]

Ihee and his coworkers have demonstrated an interesting morphological transformation between nanowires and nanotubes based on the self-assembly of diphenylalanine.[136] Nanotubes have been obtained by dissolving the peptide in water by sonication followed by heating, whereas nanowires have been obtained in water at high ionic strength. These two morphologies can be interconverted.[136] Nanotubular morphologies can be obtained by sonication and heating of the dispersed nanowires in water. On the other hand, nanowire morphologies have been obtained by dissolving the dried nanotubes in TFA and later titrating the solution with NH_4OH.[136]

So far, the morphological transformation from one nanostructure to another nanostructure has been discussed, where the basic peptide-based building blocks are unchanged. Depending on conditions such as pH, concentration, salt concentration and others, a nanostructural transition occurrs. However, by slightly varying the molecular structure in a self-assembling peptide system, nanostructural transformation has also been reported.[126,137] Gazit and his co-workers have reported a dipeptide-based nanotube to hollow nanocage structural transition by simply attaching a thiol group at the terminal position of the dipeptide.[126] It is reported that diphenylalanine (Phe-Phe), can be self-assembled in 1,1,1,3,3,3-hexafluoro-2-propanol to form a peptide nanotube. A slight change in the building block from diphenylalanine to diphenylglycine forms remarkably stable nanospheres with diameters of 10–100 nm under the same solution conditions.[126] Lu and his coworkers have reported that structural transitions (sheets, fibers, worm-like micelles, and short rods) can be influenced by increasing the hydrophobic peptide region in a series of peptide surfactant systems.[137]

11. Conclusions

The making of peptide-based specific nanostructures (e.g., nanotubes or nanovesicles) using controlled self-assembly under appropriate conditions still remains a challenging task. This is due to the fact that nanostructural transformation from one nanoscopic structure to an other sometimes occurs, or a mixture of nanostructures (like nanotubes and nanovesicles) can be obtained in the process of preparing a specific nanostructure with desired dimensions in an aqueous solution. So, the proper choice of peptide based building blocks is not the only determining factor for a specific type of nanostructure; the appropriate conditions (concentration, pH, solvent and others) can also play a vital role in determining a particular type of self-assembling pattern which can give rise to a specific type of nanostructure (e.g., a nanotube or a nanovesicle or a mixture of both). Vesicles and nanofibrillar gels are attractive targets for making nanobiomaterials drug delivery vehicles. The proper selection of peptide-based molecular building blocks and the tuning of the self-assembling pattern under appropriate conditions still remains a challenging issue in making the desired peptide-based vesicular or fibrous gel-based nanobiomaterials that can carry some bioactive molecules as cargo to the targeted site. So, it is important to make vesicular assemblies or nanofibrous gels with a peptide sequence that can be targeted towards a specific location inside the cell. The peptide-based porous materials can be biodegradable compared to conventional porous materials. Controlling the porosity of self-assembling peptide-based nanoporous material is also challenging. It is necessary to obtain a short peptide-based porous material with a well-defined nanoscale dimension and to modulate its porosity, so that the porous material with a smaller pore size can only adsorp gases with a small molecular dimension (e.g., H_2) from a mixture of gases selectively.

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