Self-assembling peptide nanotubes

Biological proteins and peptides have the intrinsic ability to self-assemble into elongated solid nanofibrils[1–7], which may give rise to amyloid diseases[8–11] or inspire applications ranging from tissue engineering to nanoelectronics[12–16]. Proteinaceous fibrils are extensively studied and well understood, to the extent that detailed theoretical models have been proposed that explain and predict their behavior[17,18]. Another intriguing state of protein-like self-assembly is that of nanotubes (NTs), defined here as an elongated nano-object with a definite inner hole. In contrast to proteinaceous fibrils, nanotubes are much less frequently observed and far less well understood. However, they have attracted research interest internationally as key components for nanotechnology.

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Peptide nanotubes

Nanotubular structures can form from a variety of different materials such as inorganic[19–22], carbon[23], biological microtubules, porins[24], viral proteins[25], α-lactalbumin[26], amyloid proteins[27], DNA[28,29], lipids[30,31] carbohydrates[32–34], synthetic polymers[35], and other organic systems[36–44]. Molecular self-assembly is the main bottom-up approach[45] for the affordable production of bulk quantities of well-defined nanostructures. Biological building blocks such as DNA, lipids, and viruses[46] are extensively studied for this purpose.

Proteins and peptides are the most versatile natural molecular bricks, due to their extensive chemical, conformational and functional diversity[47,48]. They also offer specificity of interactions, necessary for biosensing, catalytic and molecular recognition processes, and scalable production either through chemical synthesis or genetic engineering. Due to the high complexity of proteins, there is a difficulty associated with the thorough understanding of the physical and chemical principles that underpin and control their self-assembling properties. Simple model systems and short peptides offer a much more viable route to gaining a quantitative and systematic insight into protein-like self-assembly. Here we review the emerging field of self-assembling nanotubes made of simple peptide building blocks, and discuss their morphologies, applications and the future outlook. We start with the simplest systems and work towards increasingly complex systems.

Dipeptides

The simplest peptide building blocks for the construction of NTs are dipeptides from the diphenylalanine motif of the Alzheimer's

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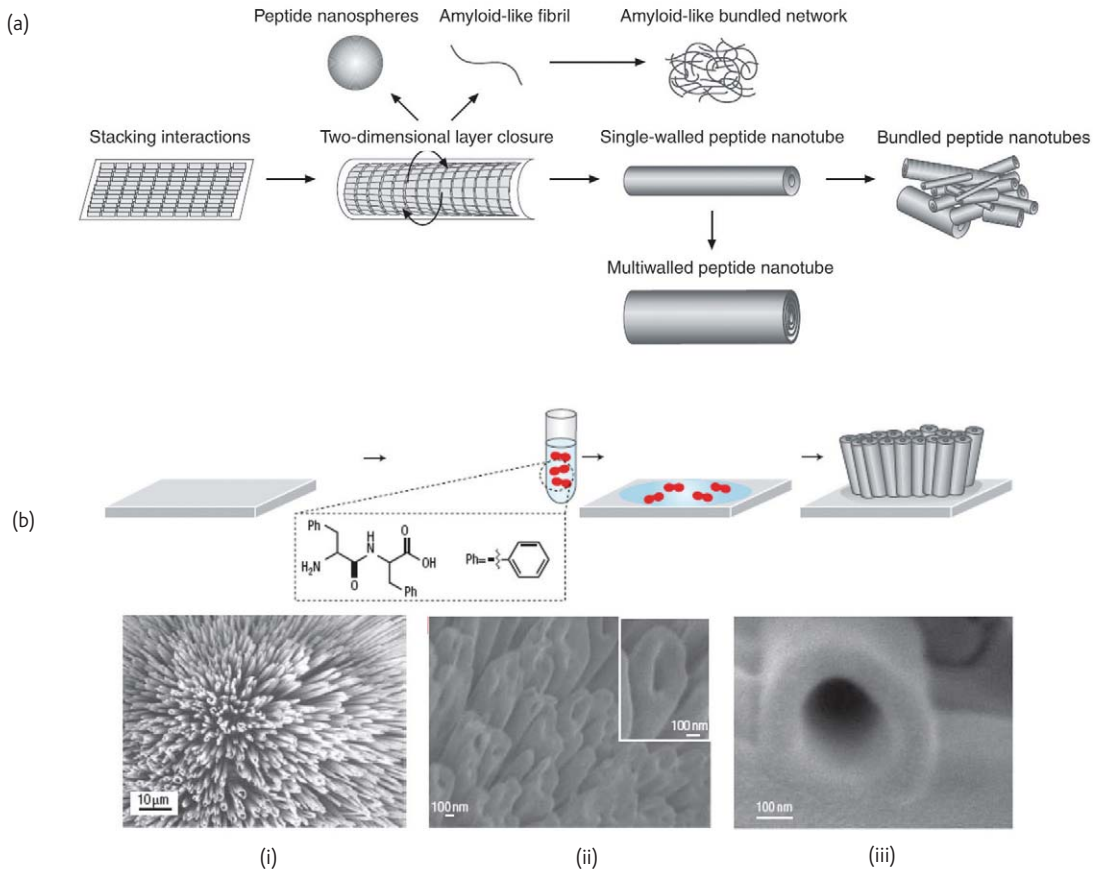

Fig. 1 (a) Schematic of the formation of tubular (single or multiwalled), spherical, or fibrillar structures via dipeptide self-assembly. (b) Proposed model for the formation of aligned peptide nanotube arrays. (i) Scanning electron micrograph of the vertically aligned peptide nanotubes. (ii) Cold field-emission gun high-resolution scanning electron (CFEG-HRSEM) micrograph of the nanotube arrays. (iii) High-magnification micrograph of an individual nanotube obtained by CFEG-HRSEM. (Reproduced with permission from[50,60]. © 2006 IOP Publishing and Nature Publishing Group)

β-amyloid peptide[49,50]. When this peptide is dissolved at 100 mg/ml in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) and then diluted down with water at a final concentration of ≤ 2 mg/ml, multiwall NTs are formed, with a typical diameter of 80–300 nm and micron length. A similar but more rigid diphenylglycine peptide analogue forms remarkably stable spheres 10–100 nm in diameter under the same solution conditions[51]. Spherical particles also form instead of NTs when a thiol is introduced into the original diphenylalanine peptide. The occurance of either tubes or spheres provides an insight into the possible mechanism of their formation (Fig. 1a), suggesting that the formation of either tubular or closed cages by fundamentally similar peptides is consistent with the closure of a two-dimensional layer, as described both for carbon and inorganic nanotubes and their corresponding buckminsterfullerene and fullerene-like structures.

The NTs are stable under extreme conditions, e.g. in autoclave (121°C, 1.2 atm); circular dichroism spectra do not change from room temperature up to 90°C; dry tubes heated to 150°C are stable, while degradation occurs at 200°C. The NTs display remarkable chemical stability in a wide range of organic solvents and pH. Indentation atomic force microscopy experiments on the mechanical properties of dried NTs on mica[52] give an estimated averaged point stiffness of 160 N/m and a high Young's modulus of ~19 GPa (27 GPa in another study[53]). This makes them amongst the stiffest known biological materials. For example, biological microtubules which provide a rigid cytoskeleton to the cell have a Young's modulus of ~1 GPa. However, the stiffness of the dipeptide NTs is lower than that of carbon and inorganic nanotubes. It has been suggested that as well as intermolecular hydrogen bonding, the rigid aromatic side chains may also be responsible for stability and mechanical strength, as well as providing directionality for formation through specific π–π interactions. Biological systems are notorious for their instability and sensitivity to temperature and chemical treatments. The significant thermal and chemical stability of these NTs points to their possible use in micro- and nanoelectromechanics (MEMS and NEMS) and functional nanodevices.

Carbon nanotubes (CNTs) are extensively studied for sensing applications due to their mechanical stability, conductance and large surface area. A drawback of CNTs is the effect exposure to humidity,

oxygen, N_2O, and NH_3 has on their electric properties. CNTs are also believed to pose problems in device fabrication due to lack of uniformity, hydrophobicity and thus, limited solubility, reproducibility of precise structural properties, cost, and limited opportunities for covalent modification. Therefore, the dipeptide NTs offer an attractive alternative for device fabrication. Several steps have been taken in this direction. In one example, peptide NTs have been deposited on graphite electrodes[54]. Improved electrode sensitivity is observed, suggesting that this may be due to an increase in the functional electrode surface in the presence of NTs. In a related study, thiol-modified peptide NTs have been immobilized and dried on Au electrode surfaces and an enzyme coating was applied to them[55]. The resulting electrodes show improved sensitivity and reproducibility for the detection of glucose and ethanol, short detection time, large current density, and comparatively high stability. The findings show that novel electrochemical biosensing platforms may be fabricated based on biocompatible NTs.

Cationic dipeptides NH_2–Phe–Phe–NH_2 self-assemble into NTs at neutral pH and rearrange into spherical structures (possibly vesicles) ~ 100 nm in diameter, upon dilution below 8 mg/ml[56] (Fig. 2). The tubes can be absorbed by cells through endocytosis upon spontaneous conversion into vesicles. This property has been used to deliver oligonucleotides into the interior of the cells as a proof of concept of the potential applications of the system in gene and drug delivery.

Dipeptide NTs have also been used to fabricate 20 nm Ag nanowires, effectively acting as a degradable casting mould[57]. Ag ions are reduced to metallic Ag in the lumen of the tube, and the peptide template removed by enzyme degradation. This approach may have applications in molecular electronics as such small nanowires cannot be made by conventional lithography. In another related study[58], $AgNO_3$ is reduced in the hollow pores of the NTs, then thiol-containing linker peptides are bound on the outside of the nanotubes. These attached Au nanoparticles, which act as nucleation sites during the electroless deposition of a gold, cover the NTs. Thus the fabrication of metal-insulator-metal trilayer coaxial nanocables, which may give rise to unique electromagnetic properties, has been demonstrated.

In many applications, nanotubes cannot be applied as individual nanostructures, rather their macroscopic organization is necessary or preferred. Using a simple method, two-dimensional ordered films of NTs ~1 μm in thickness have been created, comprising closely arranged spherulites of multiple NT bundles[59]. This is achieved by dissolving the NTs in the carbon-nanotube-debundling solvent N-methyl-2-pyrrolidone (NMP), followed by deposition of the peptide solution on a surface (SiO_2, Au, Pd, alumina, mica, quartz, InP), heating at 60°C for solvent evaporation, and cooling to room temperature. Successful preparation of a Ag-embedded NT composite network has also been carried out using a similar approach. The authors intend to expand these experiments to form other hybrid films, thus offering opportunities for the construction of new complex nanostructures, for use in biosensors and biocoating materials.

Impressive macroscopic alignment (Fig. 1b) has also been demonstrated by nanoforests of vertically aligned NTs, formed by unidirectional growth of dense arrays[60]. This process involves application of the dipeptide dissolved in HFIP onto siliconized glass followed by solvent evaporation. It has been proposed that evaporation results in a super saturation state that facilitates the formation of numerous nucleation sites on the surface. This may then be followed by unidirectional growth of nanotubes as more peptides join the growing ends of the tubes. A method for horizontal alignment of NTs has also been demonstrated through non-covalent coating of the tubes with magnetite nanoparticles and the application of an external magnetic field. These results demonstrate the ability to form a two-dimensional dense array of these NTs with either vertical or horizontal patterns.

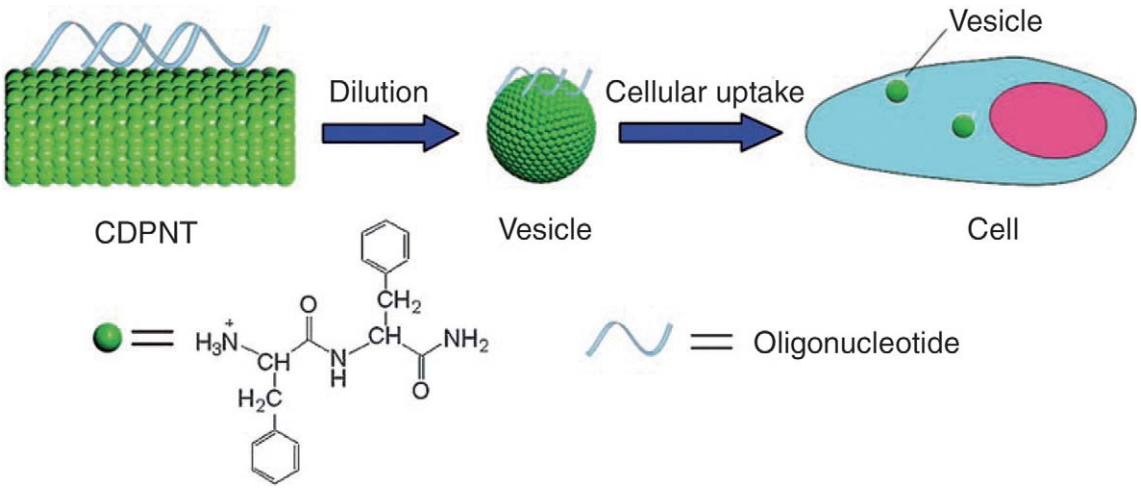

Fig. 2 Proposed model for the transition of DNA-loaded cationic dipeptide nanotubes (CDPNTs) into vesicles and their cellular uptake for oligonucleotide delivery. (Reproduced with permission from[56]. © 2007 Wiley-VCH.)

Linear peptides

Next up in molecular complexity are longer designed peptide surfactants approximately 2–3 nm in length, with a hydrophilic head of one or two charged amino acids and a hydrophobic tail of four or more consecutive hydrophobic ones, e.g. A_6D, V_6D, G_8DD, KV_6[61–63]. Upon dissolution in water at 4–5 mM, these peptides form a network of cationic or anionic open-ended nanotubes (Fig. 3) with 30–50 nm diameters and numerous three-way junctions that connect them together; vesicles can fuse or bud out of the nanotubes. The 4–5 nm thick wall is formed by a bilayer of peptides. These tubes are stabilized by hydrophobic effects and they are reminiscent of the nano- and microtubes formed by lipids, but an order of magnitude smaller in diameter. However, unlike conventional surfactants, peptide surfactants pack by hydrogen bonding interactions. In fact, some peptide surfactants display typical β-sheet structure implying a fairly extended backbone. pH is also an important factor since the charge needs to be maintained in the headgoups, to avoid conversion of NTs into large membranous aggregates. Peptide purity is also found to be crucial for the reproducible behavior of peptide NTs[64].

Alanine (A) and valine (V) produce more homogeneous and stable NTs than glycine (G), isoleucine (I), and leucine (L). For cationic peptides, lysine (K) or histidine (H) are preferred over arginine (R), possibly due to steric effects[65]. Glycine and aspartic acid (D) are also interesting because these amino acids are believed to have been present in the prebiotic environment of the early Earth. If peptides consisting of a combination of these amino acids can form nanotubes and vesicles, they would have the potential to provide primitive enclosures facilitating catalysis and prebiotic molecular evolution[66]. It is also possible to design molecular recognition elements into the peptide, in order to deliver a wide range of substances inside the cell in a site-specific manner. Envisaged applications include carriers for the encapsulation and delivery of a number of small, water-insoluble molecules and large biological molecules, including negatively charged nucleic acids inside the cell, and cosmetic applications.

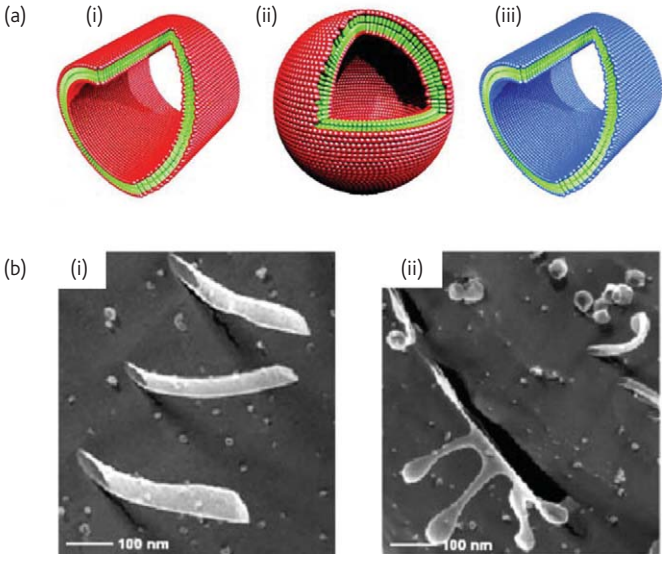

Fig. 3 (a) Self-assembling nanotubes and vesicles of negatively and positively charged surfactant peptides: (i) V_6D nanotubes; (ii) V_6D vesicles budding out of nanotubes; and (iii) K_2V_6 nanotubes. Color code: green-hydrophobic tails, red-aspartic acid, blue-lysine. (b) Quick-freeze/deep-etch transmission electron micrographs of (i) surfactant peptide nanotubes; (ii) vesicles possibly budding from the nanotubes or vice/versa. (Reproduced with permission from[63]. © 2006 Springer)

A biological peptide derived from the amphiphilic core Aβ(16-22) of the Alz peptide can also assemble into parallel β-sheets that produce bilayer structures at low pH (Fig. 4a). These stack on top of each other in large numbers to give rise to helical ribbons which fuse at the edges to produce highly homogeneous nanotubes (Fig. 4b) with a 52 nm outer diameter, a 4 nm-thick wall and lengths of several microns[67,68]. The tubes can be densely coated with negatively charged colloidal Au particles to prevent further NT association. Extensive bundling (diameter of ~1 μm and >5 mm contour length) of NTs can be achieved by salting out (Fig. 4c and 4d). Counter ion mediation allows lateral alignment of the NTs during this process. This is a simple and generic strategy to produce higher order assemblies of homogeneous NTs.

Chemically modified linear peptides

Nonbiological modifications of linear peptides can help tip the balance towards the formation of hollow nanotubes as opposed to solid nanofibrils. Three notable examples illustrate this point. The first example comes from the 20–29 segment of amylin protein which undergoes amyloid β-sheet fibrillization. Several derivatives of this segment have been produced with a modified backbone to prevent intermolecular hydrogen bonding and thus act as β-sheet breakers, and abolish fibril formation[69]. Unexpectedly, two of these derivatives form helical ribbons and NTs 200–300 nm in diameter and several microns in length. The increased hydrophobicity of these derivatives, as opposed to intermolecular backbone hydrogen bonding, is believed to be the driving force for self-assembly in this case.

In the second example, studies focused on a model peptide show the formation of solid β-sheet fibrils. Variant biotinylated peptides designed with different linkers between biotin and the peptide termini are shown by fourier transform infrared (FTIR) to adopt β-sheet structure and to form homogeneous tubes in water with an external diameter of 60 nm and an internal diameter of 30 nm[70]. The antibiotin antibody effectively binds to biotin groups on the NTs. The authors propose using these tubes as scaffolds for proteins. In a recent study[12], short peptide derivatives (N-(fluorenyl-9-methoxycarbonyl) commonly known as Fmoc, Fmoc-Leu_2 and Fmoc-Leu_3, have also been shown to form gels in water consisting of nanotubes with external and internal diameters of 15.2–19.5 nm and 4–6 nm, respectively. Interestingly, they were twisted into two-dimensional β-sheets by enzymatically triggered self-assembly.

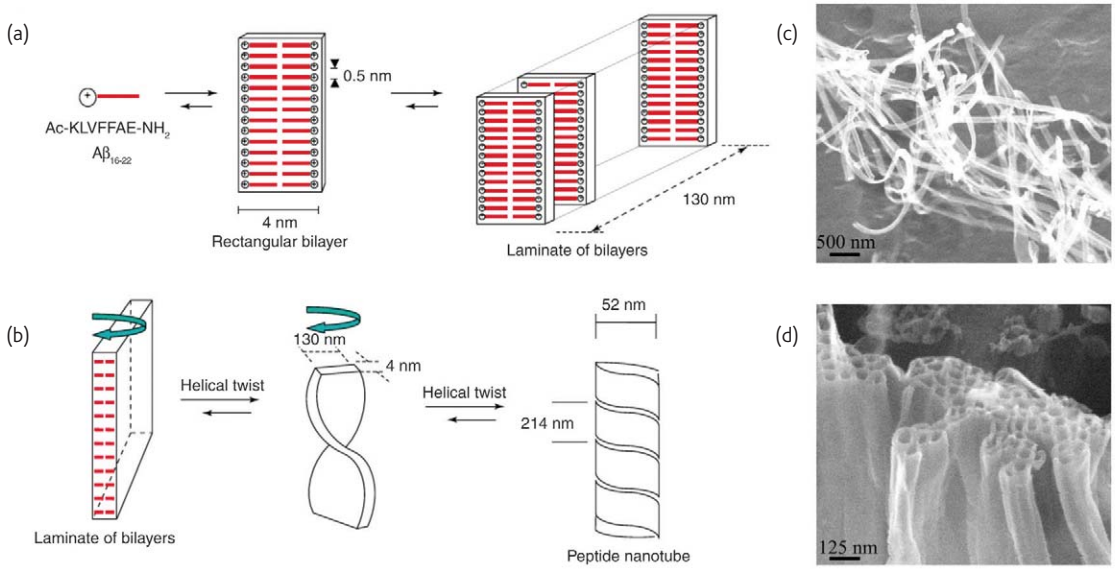

Fig. 4 Proposed model for self-assembly of Aβ(16–22) peptide nanotubes. (a) A flat rectangular bilayer stacks to form a laminate of bilayers. (b) The laminate of bilayers twist to form nanotubes. Cryo-etch high-resolution SEM micrographs of peptide nanotubes: (c) before, and (d) after sulphate bundling. (Reproduced with permission from[14,67]. © 2004 and 2007 Elsevier and The Royal Society of Chemistry)

A class of well-studied NT-forming molecules containing both peptidic and non-peptidic segments are the bola-amphiphilic peptides (Fig. 5a), which over the course of several days in water, form NTs (Fig. 5b) with a wide range of diameters from 20 nm to 1 μm[71]. In order to control their diameter, NTs have been assembled within polycarbonate membranes[72]. Depending on pore size, the membrane can act as a template to produce NTs with a controlled width from 50 nm to 1 μm. This opens up the opportunity to apply NTs as templates for nanowires. Nanowires are essential building blocks for electronics and sensors; production of nanowires of uniform diameter is crucial for these applications as their electric and magnetic properties are sensitive to size. In one study, NTs have been immobilized on self-assembling monolayer (SAM)-functionalized Au substrates via hydrogen bonding and then metallized by nickel[73]. This approach may be useful for nanoelecronic fabrication since the NTs can be coated with various metals to form metallic nanowires.

NTs have also been functionalized with proteins, nanocrystals, and metalloporphyrin coatings via hydrogen bonding[74]. The application of these coated tubes to nanoscale, highly sensitive chemical sensors, electronics or photonics may be possible. In another study, a model lipase enzyme is encapsulated in NTs by incubation for a week[75] (Fig. 5c). The catalytic activity of the nanotube-bound lipase increases by 33% as compared with free-standing lipases at room temperature. At elevated temperatures of 65°C, the lipase activity inside the NTs is 70% higher than free standing lipases. These amazing results are believed to stem from the fact that the bound lipase activity is most likely induced by the conformational change of lipases to an enzymatically active structure during adsorption.

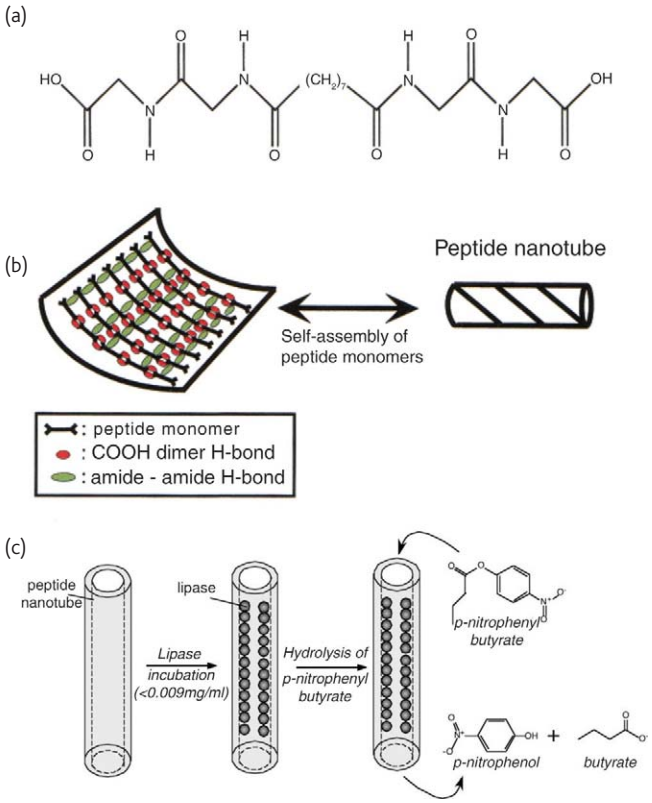

Fig. 5 (a) Chemical structure of the bola-amphiphilic peptide monomer, bis-(N-R-amido-glycylglycine)-1,7-heptane dicarboxylate. (b) Proposed model for the formation of peptide nanotubes. (c) Schematic illustrating the formation of lipase-loaded peptide nanotubes and their enzymatic application. (Reproduced with permission from[71,75]. © 2001 and 2005 American Chemical Society)

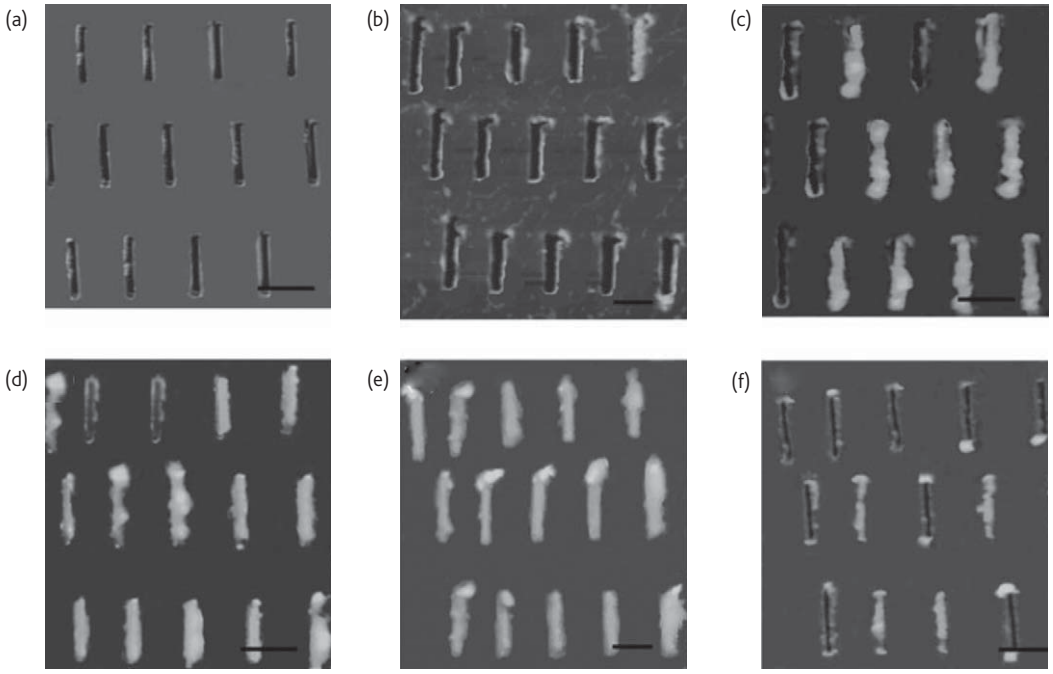

Fig. 6 Atomic force microscopy of antihuman-IgG-coated bolaamphiphilic peptide nanotubes attached to trenches filled with human IgG (a) before incubation with antibody-coated nanotubes – 0%, (b) when the concentration of human IgG is 70% with 30% of BSA spacer on the trench. (c) When the concentration of human IgG in the trench is reduced by 50%, antibody-nanotube attachment improves dramatically. (d) The trend continues even at a reduced concentration of 10% human IgG. (e) Maximum nanotube attachment is achieved when the concentration of human IgG in the trench is 7%, and (f) at human IgG concentrations < 7%, nanotube attachment decreases by 3%. Scale bars=500 nm. (Reproduced with permission from[77]. © 2007 Wiley-VCH.)

This class of NTs can also be organized macroscopically, e.g. Ni^{+2} ions employed as a bridge between free peptide amines result in bundles (diameter 100 μm and length 3 mm) of NTs. Addition of EDTA to the suspension causes disassembly of the NT bundles. Bundles will have greater mechanical stability than individual ones, which may be necessary for applications. They are also easier to handle than individual NTs. Another important property for application development is the ability to immobilize NTs at a specific location on a substrate. Accurate localization of NTs can be demonstrated by assembling antibody-functionalized NTs at specific locations on substrates (Fig. 6) where their complementary antigen proteins are patterned[76,77].

Cyclic peptides

Self-assembling NTs based on a variety of cyclic peptides[78–83] have been reported. A well-characterized example is the naturally occurring Lanreotide growth hormone inhibitor peptide (Fig. 7a). When dissolved in water, it adopts a closed compact β-hairpin-like conformation through a disulphide bond (Fig. 7b). At a peptide concentration of 3–20% wt/wt, a gel is formed. In these conditions, self-assembly into a bilayer is observed, consisting of amphiphilic β-sheets with systematic segregation of aromatic and aliphatic side chains. Thus, the hydrophobic effect generates a bilayer, while intermolecular backbone hydrogen bonding causes assembly of peptides in one dimension into long ribbons. Finally, the hydrophobic effect between the edges of the ribbons stabilizes lateral association of 26 ribbons to form the wall of the nanotube (Fig. 7c). This process gives rise to hexagonally packed, highly monodisperse long NTs with a diameter of 24.4 nm and a wall thickness of 1.8 nm[84,85] (Fig. 7d–f).

By far the most extensive literature on cyclic peptide NTs is devoted to the molecules designed in Ghadiri's laboratory[86]. These cyclic peptides have an even number of alternating D and L amino acids, and stack through extensive intermolecular hydrogen bonding to form long cylindrical structures with an anti-parallel β-sheet structure. The outer surface of NTs is defined by all the amino acid side chains and thus can be controlled by peptide design[87], or by covalent incorporation of polymers, producing polymer shells around the NTs[88,89] (Fig. 8). The ability to tune the outer surface properties enables NT formation in a variety of different environments, such as in bulk solution, in the solid state (crystals of regularly packed nanotubes), and as transmembrane pores inside the cellular lipid bilayer that can act as efficient ion channels. The pores can be preferentially assembled inside bacterial rather than eukaryotic cell membranes and cause bacterial death through osmotic collapse. This work has led to the development of new antimicrobial and cytotoxic agents, controlled-release drug delivery carriers, and new artificial ion channels whose transport properties are tuned by peptide design. The internal diameter of these NTs is completely uniform and can also be adjusted by peptide design.

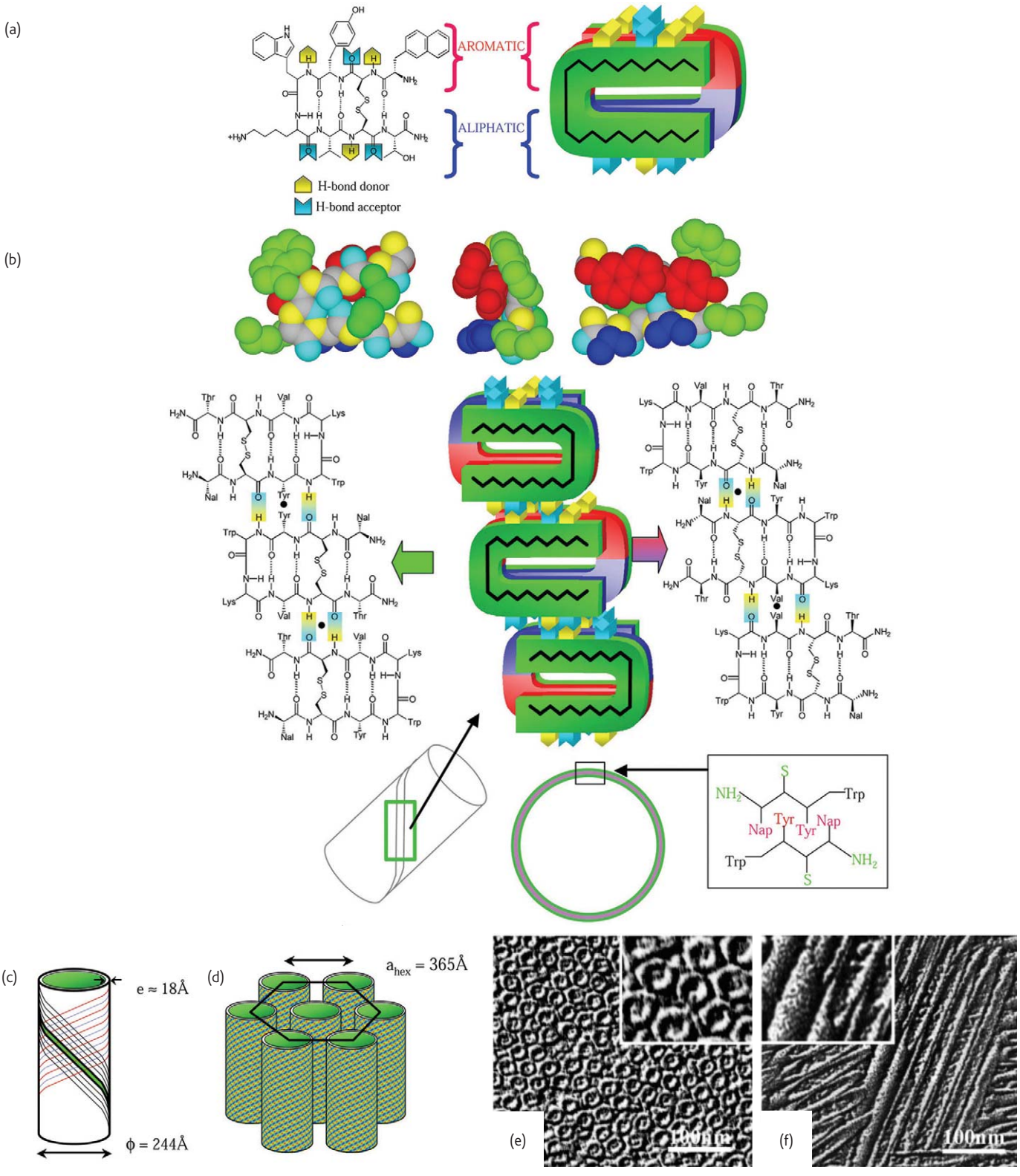

Fig. 7 Lanreotide-acetate peptide nanotubes in water. (a) The molecular structure is a β-hairpin conformation stabilized by the disulfide bridge. (b) One-dimensional self-assembly of a ribbon made of two stacked β-sheets. (c) Lateral assembly of 26 ribbons to form a nanotube. (d) Liquid-crystalline hexagonal columnar phase. (e) Freeze-fracture electron micrographs of a 14% wt/wt sample, perpendicular, and (f) parallel to the direction of the nanotubes. (Reproduced with permission from[85]. © 2003 National Academy of Sciences.)

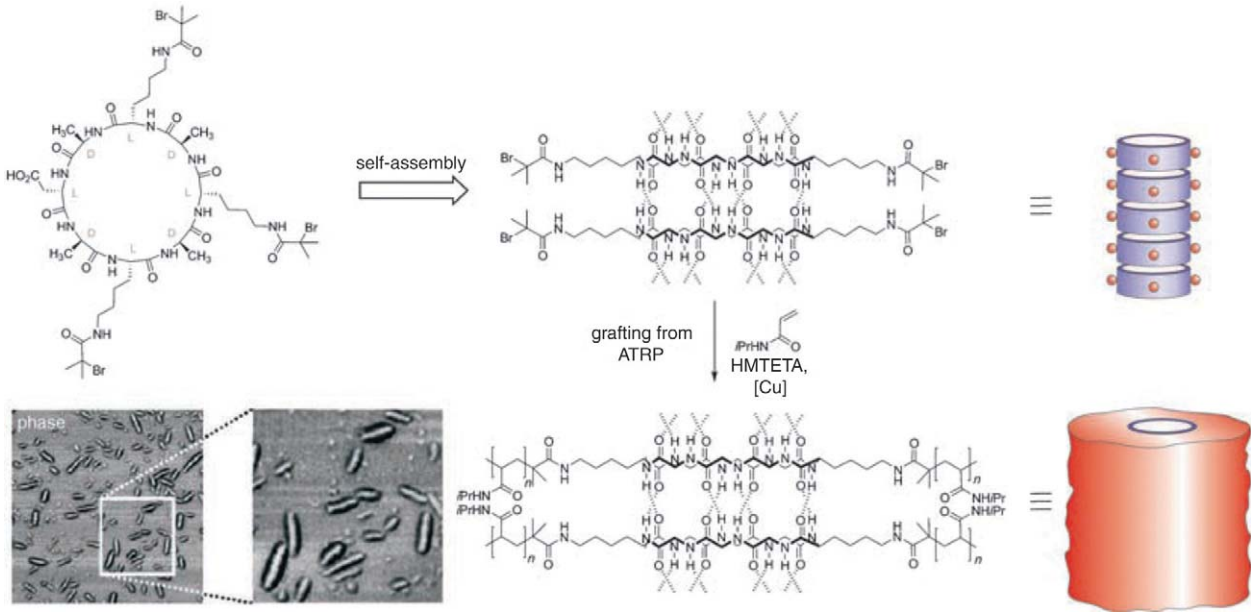

fig. 8 Grafting a polymer shell on preassembled cyclic peptide tubes: D,L-Cyclo-α-peptides carrying initiator groups stack to form tubular structures from which N-isopropylacrylamide (PNIPAM) is grown by atom-transfer radical polymerization (ATRP); HMTETA=1,1,4,7,10,10-hexamethyltriethylene. AFM images depict the peptide-PNIPAM hybrids (scales: 2 mm and 800 nm). (Reproduced with permission from[88]. © 2005 Wiley-VCH.)

Systematic studies reveal that cyclic octapeptides exhibit good rigidity and predisposition for tubular assembly with a van der Waals internal diameter of 7 Å and can transport K^+ and Na^+ across the lipid bilayer. A cyclic decapeptide NT possesses a 10 Å van der Waals internal diameter and transports larger molecules such as glucose, while the smaller octapeptide lacks such activity. A cyclic dodecapeptide NT has an internal van der Waals diameter of 13 Å[90].

Non-biological applications of the NTs have also been examined. Elucidation of the electronic properties of these nanotubes suggests a wide highest occupied molecular orbital–lowest unoccupied molecular orbital (HOMO-LUMO) gap for the nanotubes, of interest to bioelectronic device applications. Unmodified peptides are electronically insulating as are most biomaterials made of natural amino acids. In a recent study, cyclic peptides have been designed bearing four cationic 1,4,5,8-naphthalenetetracarboxylic groups (NDI). These molecules undergo redox-triggered self-assembly in aqueous solution into long peptide NTs that possess highly delocalized electronic states[91]. The cyclic peptide assembly here is used as a scaffold to promote stacking of NDI groups and charge transfer between them and to provide ordered electronically active biomaterials with potential utility in optical and electronic devices.

Outlook

A wealth of stable nanotubes form from simple peptide building blocks, ranging from 0.7 nm to 1 000 nm in diameter and of varying rigidities. The shortest peptides (dipeptides) form the widest NTs, while the narrowest NTs are prepared by cyclic peptides. Control of surface properties has been demonstrated, however, in almost all the cases the inner and outer surfaces of NTs are the same and it does not seem possible to modify them independently of each other. Cyclic peptide NTs are a notable exception. Here the inner surface is always the same since it is defined by the peptide backbone, while the outer surface is distinctly different, lined by the side-chains and tunable by peptide design.

Another crucial issue in device fabrication is the ability to gain precise control over the positioning of the nanostructures relative to a substrate, to each other, and to other functional components. Significant progress has been made in this domain, but further developments are needed. However, it is obvious that the current state-of-the-art in peptide NTs already offers a wide range of morphologies, chemistries, and macroscopic arrangements to hopefully match the requirements of specific applications. This is possibly the reason why there seems to be an extensive and impressive array of applications that are currently explored using peptide NTs, such as drug delivery, biosensors, biomolecular filters, scaffolds, and microelectronics.

Despite the numerous investigations on peptide NTs, there is a need to expand studies to other factors that can determine potential commercial usefulness, such as compatibility with the final product formulations, processability, and robustness during processing. Another area that seems less advanced is the assessment of biocompatibility of peptide NTs; ideally such studies, together with rigorous quality control and peptide purification, should go hand-in-hand with the parallel escalation of their applications. Another remarkable observation is that most reported peptide NTs (apart from the cyclic peptide ones) seem to have started out as a serendipitous observation, i.e. the

researchers stumbled on them during the course of other studies. This demonstrates that we understand very little about peptide NTs, so are often not in a position to design the final product of an experiment. There also seems to be a notable lack of theoretical insight into peptide NT formation. This can be a very fruitful approach in that it captures the knowledge generated by experiments with the aim of efficient future quantitative predictions, rational design, and precise control of the properties of the self-assembling structures. nt

Acknowledgments

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