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Programming supramolecular peptide materials by modulating the intermediate steps in the complex assembly pathway: Implications for biomedical applications

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Abstract

Self-assembling peptides form a prominent class of supramolecular materials with in general good biocompatibility. To afford better control over the material properties, tremendous progress has been made in studying the supramolecular organization of the peptide assemblies. This knowledge has helped us to understand the correlation between the molecular structure of the peptide building blocks and the properties of the supramolecular products. However, peptide self-assembly consists of a complex pathway rather than a spontaneous thermodynamic process. This implies that the outcome of the self-assembly is critically governed by the assembly pathway. Here, we are going to discuss how peptide self-assembly can be modulated at the intermediate steps in the self-assembly pathway. The focus will be to demonstrate this engineering approach on the example of zero-dimensional/one-dimensional nanostructure selectivity over the β-sheet assembly pathway. In addition, we provide examples of biomedical applications of such steered peptide assemblies in the field of drug delivery and tissue engineering.

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Peptide self-assembly, Biomaterials, Supramolecular chemistry, Tissue engineering.

Introduction

Supramolecular materials with biomimetic properties are fabricated by manipulating noncovalent interactions such as hydrogen bonding, van der Waal's forces, and electrostatic interactions. Self-assembling peptides form a prominent class of supramolecular materials that have in general good biological compatibility. Self-assembling peptides can form supramolecular structures at different length scales, such as zero-dimensional (0D) micelles or vesicles and one-dimensional (1D) nanofibers or nanotubes, through a combination of side-chain and backbone interactions. The formation of secondary structure in peptides (α-helix or β-sheet) is a common molecular transition that drives controlled peptide supramolecular assembly, with cross-β [1] and coiled-coil structures [2] as two notable examples of the resulting molecular arrangement. These supramolecular assemblies have been explored for different biomedical applications including the formation of discrete nanoparticles for drug delivery [3–9] and scaffolds for regenerative medicine and tissue engineering [10–13].

There is currently a good number of experimental accounts investigating the supramolecular organization of the final structure of peptide assemblies, which has offered us atomic insights into the peptide interaction within these supramolecular structures [1,11,14,15]. However, for supramolecular peptide structure, rather than a spontaneous thermodynamic process, their assembly pathway is signified by its high complexity, along which metastable intermediates are formed before eventual conversion to the more thermodynamically stable end products [16,17]. This implies that the outcome of the peptide assembly process is critically governed by the self-assembly pathway that is being followed and thus can be influenced by directly modulating these intermediate steps [18–20]. Indeed, this explains why, although cross-β fibers are in general the most thermodynamically stable structural organization in physiological condition [21], we are still capable to access a variety of peptide assemblies with alternative structural ordering, such as coiled-coil nanofibers [14].

Currently, several excellent reviews have discussed the biomedical applications of self-assembling peptide nanomaterials [22–24]. However, comparatively few

have discussed the biomedical implications in light of the complex assembly pathway. Here, on the example of β-sheet peptide assemblies, we will demonstrate how manipulating the complex peptide self-assembly pathway can afford better control over the structures and properties of the resulting materials. Because the kinetic pathways of β-sheet assembly are highly complex [25], to stay focused to the objective of this review, we have chosen to exemplify this engineering approach with the 0D/1D nanostructure selectivity over the β-sheet assembly pathway (Figure 1), as nanostructures at these length scale are widely used in biomedical application [26]. Subsequently, we will discuss the common approaches used to modulate the self-assembly pathway. Finally, we will highlight the possibilities and considerations for the biomedical application of peptide nanostructures in light of the pathway complexity.

Parallel and competing kinetic pathways of 0D and 1D nanostructures formation

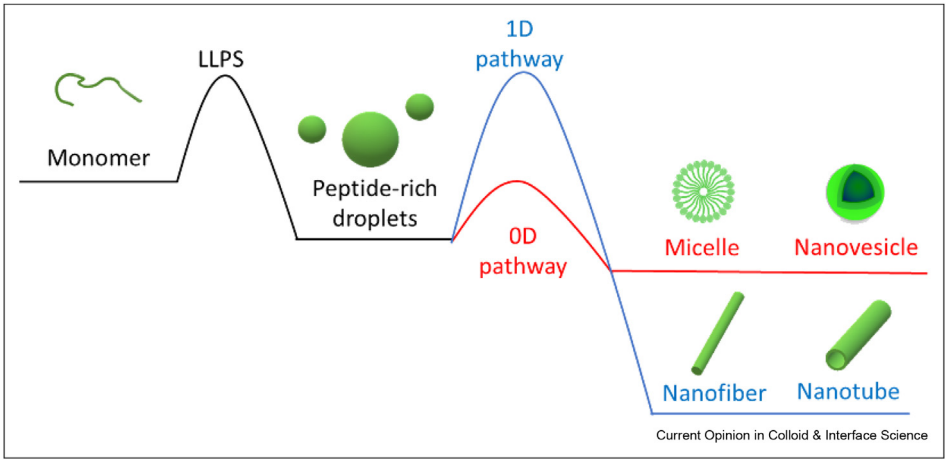
Liquid–liquid phase separation as the common first step before pathway divergence

Unlike supramolecular structures composed of low molecular weight polymers, peptides possess a relatively large desolvation barrier in water, which makes it energetically improbable to spontaneously assemble into ordered structures. To overcome the desolvation barrier, liquid–liquid phase separation (LLPS) is a common first step in peptide self-assembly [17,27,28] (Figure 2a and b). The LLPS process is entropically driven, in which the entropic gain is rooted from the increase in peptide conformational freedom and the gain of water entropy through peptide desolvation [27]. The LLPS process will lead to formation of peptide-rich droplets, or oligomeric particles, which create an alternative environment for peptide arrangement into more ordered assemblies [28–30]. Recent work by Michaels et al. [29] has outlined the probabilistic nature for the assemblies to progress through different stages of the assembly pathway. In section 3, we are going to describe the common strategies to direct the assembly process toward the particular kinetic pathway.

Zero-dimensional nanostructure pathway selection if no cross-β nucleates are formed

Cross-β nucleation is the critical event that decides the bifurcation between the 0D and 1D nanostructure assembly pathways. If no cross-β nucleate is formed, the oligomeric particles will transform into 0D nanostructures (e.g. micelles [6,31,32] and nanovesicles [33,34]). Our group has previously integrated state-of-the-art experimental techniques with large-scale and multiscale molecular dynamic simulation to elucidate the self-assembly pathway of an amphiphilic peptide (SA2: Ac-AAVVLLLWEE-COOH) that will form nanovesicles when dispersed in aqueous media [33]. In good agreement with recent *in situ* studies on amphiphilic self-assembly [35], we have detected that the oligomeric particles condensed via LLPS adopt a micellar arrangement. The micellar oligomers will then grow by monomer addition and evolve into elongated micelles, followed by the formation of interdigitated bilayers and disks, and eventually into water-filled hemispheres [33] (Figure 2b). Interestingly, structural analysis of these 0D nanostructures revealed that, although they are not following templated elongation with cross-β nucleates, the orthogonal β-sheet pattern (interstrand distance at ~4.7 Å, intersheet distance at ~10 Å) could still be observed [6,33]. This implies that cross-β interactions also contributed to the structural organization in these assemblies, but with lower periodicity than 1D nanostructures.

Figure 1



Schematic representation of the complex pathway of β-sheet peptide self-assembly that direct formation of 0D nanostructures (e.g. micelle, nanovesicle) and 1D nanostructures (nanofiber, nanotube). LLPS: liquid–liquid phase separation; 0D: zero-dimensional; 1D: one-dimensional.

The hierarchical pathway for 1D nanostructure formation

One-dimensional nanostructure pathway selection through formation of cross-β nucleates

Formation of cross-β nucleates in the oligomeric particles can trigger the hierarchical assembly of cross-β fibers (Figure 2a). As described earlier, the cross-β structures are signified by orthogonal β-sheet interactions, characterized by a distinctive X-ray diffraction pattern with reflection at ∼4.7 Å that represents the inter−β-strand repeats and a perpendicular reflection at ∼10 Å that represents the inter−β-sheet repeats [1]. Formation of cross-β nucleates within the oligomeric particles is an enthalpy-driven process; the entropic penalty (increased molecular order) is compensated by the enthalpic gain of the cooperative noncovalent interactions (hydrogen bonding, van der Waal's forces, electrostatic interactions) [27]. Nucleates are formed when a critical number of cross-β−arranged peptides is reached [28]. After reaching that threshold, replication of the cross-β molecular ordering thereafter will become energetically favorable [36]. The propensity of cross-β nucleation is influenced by the sequence length, β-sheet propensities and side-chain molecular compatibility of the peptide as well as the size of the oligomeric particles formed [28,37,38].

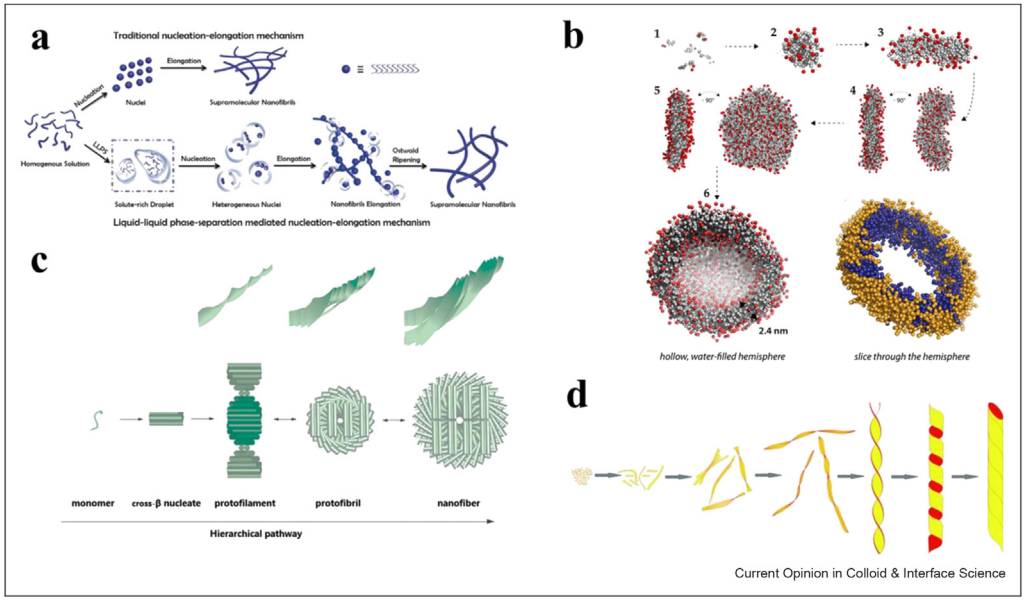
Protofilaments formation via the nucleation−elongation mechanism

Through a nucleation−elongation mechanism, the replication of cross-β molecular order will yield protofilaments, or β-sheet ribbon, as the primary units leading to the build-up of hierarchical 1D nanostructures [39]. As the lowest level structure in the assembly hierarchy, the protofilaments adopt an elementary supramolecular organization with a single cross-β interface [1]. Previous studies reveal that the prime hindrance in the elongation process is desolvating the peptide monomers [40]. Therefore, the sequence length and residual hydrophobicity of the peptides are major factors influencing the propensity of the elongation mechanism [40].

One-dimensional nanofiber pathway selection via protofilament association

After protofilaments have been formed, the next step in the hierarchical pathway is the association of protofilaments into protofibrils [39]. In hierarchical 1D nanostructures, the assembly of protofilaments is driven by the side-chain interface with higher association force; the assembly of secondary units (protofibril) is driven by the side-chain interface with weaker association force, which drives the lateral association of protofilaments. The final structure (nanofiber) is formed via the edge-to-edge β-strand interaction, which drives the

Figure 2



The self-assembly mechanisms of peptide structures **(a)** Difference in supramolecular fibrillization between small molecule supramolecular polymers (traditional nucleation−elongation) and self-assembling peptides (LLPS-mediated nucleation−elongation). Adapted with permission from Wiley Publishers Ltd: Angewandte Chemie; Yuan et al. [27] copyright (2019). **(b)** The bottom−up self-assembly mechanism of peptide nanovesicles. It shows that both nanovesicle and nanofiber pathways undergo LLPS as the first step before diverting to their respective pathway. Adapted with permission from American Chemical Society: JACS.;Rad-Malekshahi et al. [33] copyright (2015). **(c)** Hierarchical self-assembly of peptide nanofibers. Supramolecular structures with ascending structural sophistication are shown from left to right. Adapted with permission from Future Medicine Ltd: Nanomedicine; Maude et al. [22] copyright (2013). **(d)** Hierarchical self-assembly of peptide nanotubes. The self-assembly mechanisms deviate from that of nanofibers at the protofibril stage to form helical ribbon intermediates. Permission from Wiley Publishers Ltd: Angewandte Chemie; Adamcik et al. [45] copyright (2011). LLPS: liquid−liquid phase separation.

longitudinal association of protofibrils [39] (Figure 2c). Notably, because of the chemical anisotropy between side-chain (mostly van der Waal's forces) and backbone interactions (hydrogen bonding), all these filament structures are twisted [41,42]. The structural twisting can halt unlimited growth of the fibrous structures in lateral and longitudinal directions [39,42]. Previous studies has revealed that the assembled nanofibers are mainly kinetically trapped species, which shows the fiber morphology is under kinetic control, that is, the energy barrier for each step determines the resultant fiber morphology [43]. This explains why, although the chirality of natural L-amino acids should give left-handed twisted nanofibers, the twist handedness can be counteracted by the hierarchical process to generate right-handed twisted fibres [44].

One-dimensional nanotube pathway selection via formation of the helical ribbon intermediate

The 1D nanotube pathway deviates from the protofibril step in the 1D nanofiber pathway. Rather than undergoing longitudinal association, protofibrils are transformed to helical ribbon intermediates; the closure of these helical ribbons will give 1D nanotubes [45–48] (Figure 2d). The closure mechanism of the helical ribbon is a relatively slow process, which generally takes weeks to conclude [45–48]. Furthermore, the diameter of the nanotube is determined by the magnitude of the lateral interactions in the helical ribbon, which is influenced by the side-chain interface association forces [46]. Besides, 1D nanofibers are often detected alongside the nanotube structures within one supramolecular system [45,46].

Common strategies to modulate peptide assembly pathways

Internal factors

Hydrophobic–hydrophilic residue arrangement

A common approach to modulate the self-assembly pathway is to program the arrangement of hydrophobic/hydrophilic amino acids in the peptide sequence [34,46,49]. Previous studies reveal that an increase in the hydrophobic to hydrophilic ratio (i.e. increase in hydrophobicity) favors the kinetic selection of 1D nanostructures over 0D nanostructures [34]. This can be partly explained by the fact that more hydrophobic peptides generally form larger-sized oligomeric particles, which in turn increases the chance of cross-β nucleation [28]. Furthermore, the nanotube pathway is favored by increasing the repulsive forces between the protofibrils in the longitudinal direction. This can be achieved by placing mutually repulsive residues at both ends of the β-strand [46] or by endcapping the peptide to prevent electrostatic attraction between the amino- and carboxy-terminal [45]. Besides, most of the reported 0D nanovesicle-forming peptides adapt surfactant-like sequence arrangement, in which the hydrophobic and hydrophilic amino acids are arranged in two modular compartments [33,49]. The modular hydrophobic–hydrophilic pattern can likely facilitate the micelle to nanovesicle transition [35].

Molecular geometry and β-sheet propensities

Altering the molecular geometry of peptides is another approach to moderate the assembly pathway. For example, molecular geometry can be adjusted by engineering the conformational (β-sheet) propensities of the peptide sequence [50] and the molecular volume of the side-chain groups [51,52]. Increasing the β-sheet propensities of peptides can increase the probability of cross-β nucleation, thereby favoring kinetic selection of the 1D pathway [37]. The β-sheet propensities can be increased by instigating molecular frustration in peptide sequences (i.e. patterning peptide sequences with alternating hydrophobic and hydrophilic residues) [50,53,54] or incorporation of β-branched amino acids [55,56] and lowering the content of β-sheet disrupting residues, for example, proline [57]. Besides, the steric compatibility between the side-chain interface in the β-strand can also influence the propensity of cross-β nucleation [38,51,52].

Complimentary directional noncovalent interactions

The directionality of cross-β structures are conferred by the backbone–backbone hydrogen bonding interactions. The directionality can be complemented by other directional noncovalent interactions such as π-π stacking [54,58] and electrostatic attraction in the side-chain interfaces [54,59–62]. For example, Shao et al. [62] has demonstrated how the side-chain charge complementary interaction can direct a precise ABAB molecular pattern in the resultant cross-β nanofibers. Implementing these complementary interactions can therefore favor the formation of 1D nanostructures.

External factors

Solvent composition

The assembly pathway can also be extrinsically modulated through varying the solvent composition, such as the solvent polarity and pH. For zwitterionic peptides, adjusting the pH away from 7.4 can increase the mutual electrostatic repulsive force between oligomeric particles. Increase in the mutual repulsive forces can stabilize oligomeric particles at a smaller size range, which in turn lowers the probability of cross-β nucleation [28]. However, if cross-β nucleates are formed, changing the pH value can potentially alter the sequence alignment in the cross-β structures. For example, for peptides containing charged residues, changes in pH can potentially alter the electrostatic interactions between the side chains, thereby moderating the sequence alignment [59]. Such changes in sequence alignment can potentially facilitate nanotube formation through inducing longitudinal repulsive forces between

protofibrils [59,63]. With respect to organic solvents, addition of dimethyl sulfoxide [64], hexafluoro-2-propanol [6], and acetonitrile [65] can favor formation of 0D nanostructures through disrupting interpeptide hydrogen bonding networks, thereby lowering the chance of cross-β nucleation. Besides, because gain of water entropy through peptide desolvation is a major driver of LLPS [27], the rate of initial peptide solvation (e.g. rate of water addition) can therefore serve as a potential moderator of the LLPS process.

Concentration

Regarding the LLPS of peptides, the condensation process is concentration dependent [37,66]. Furthermore, like other supramolecular systems, concentration-dependent phase transition behavior is also observed in self-assembling peptides [39,48]. Higher concentrations generally favor formation of higher-order supramolecular structures. For example, Aggeli et al. [39] have demonstrated that by increasing the concentration of the P-11 peptide, 1D nanostructures with increasing sophistication of structural ordering are detected (from protofilaments, through protofibrils to fibers); Kornmueller et al. [48] have also demonstrated that a superstructure of nanofibers can be induced by increasing the peptide concentration.

Temperature and external fields

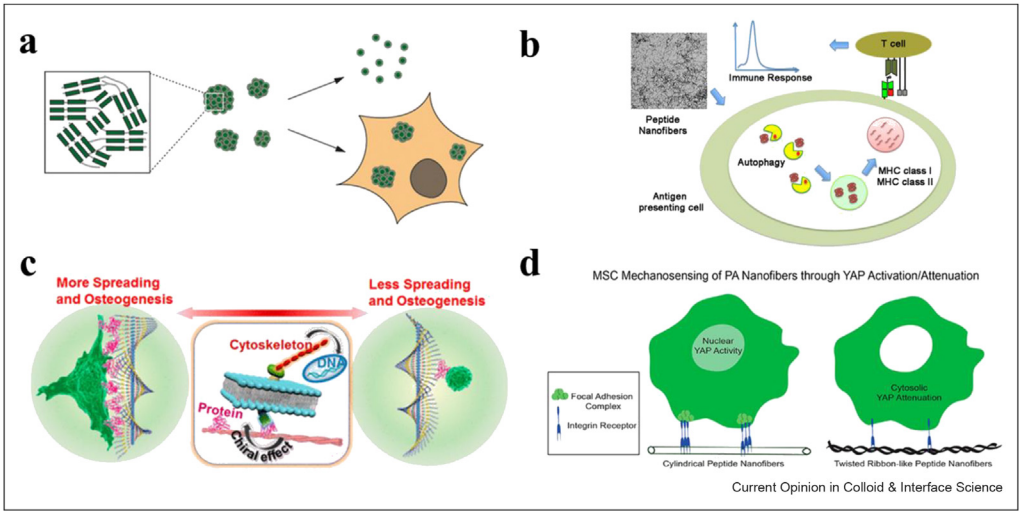
The effect of temperature is more complex. On one end, LLPS can only take place when the solution temperature drops below a certain threshold [66]. However, further reduction in temperature can freeze the molecular conformation in the oligomeric phase [37]. On the other hand, high temperatures in general disfavor the condensation process [37]; but if cross-β nucleates are formed, the increase in molecular motion can in return speed up the supramolecular polymerization process. Besides, by varying the temperature (4–37 °C), the kinetic pathways of nanofiber formation can be varied, leading to the formation of nanofibers with different morphology using the same peptide as building blocks [67,68]. Regarding external fields, such as electromagnetic fields or ultrasound, the influence of thermal effects can be referred to the aforementioned discussion on temperature. Regarding the nonthermal effects of the external fields, previous studies showed that application of electromagnetic fields can alter the β-sheet propensities [69,70] and the aggregation propensities [71] of the peptide. In addition, application of external fields can also promote directionality in molecular arrangement through peptide dipole alignment [72]. These changes can influence the likelihood of 1D nanofiber formation.

Implications for biomedical applications

Engineer nanostructures for therapeutic delivery

Both 0D and 1D β-sheet assemblies have been extensively explored for drug delivery applications, thanks to their good biocompatibility and comparatively stable

Figure 3



Biomedical application of kinetic control over self-assembling peptides. **(a)** Selective uptake of 0D peptide nanostructures to professional antigen presenting cells (e.g. macrophage and dendritic cells). Adapted with permission from American Chemical Society: ACS Nano,; Kumar et al. [6] copyright (2014). **(b)** Engagement of autophagy mechanism of 1D peptide nanofibers upon uptake by professional antigen-presenting cells. Adapted with permission from American Chemical Society: ACS Omega, Rudra et al. [83] copyright (2017). **(c)** Effect of nanofiber chirality on stem cell spreading and differentiation. The left-handed twisted nanofiber has better ability to induce osteogenesis than the right-handed twisted nanofiber. Adapted with permission from American Chemical Society: ACS Applied Materials & Interfaces; Dou et al. [87] copyright (2019). **(d)** Effect of nanofiber helicity on mechanotransduction of stem cells. The untwisted/cylindrical peptide nanofiber incur higher stem cell osteogenic potential through the activation of nuclear YAP, whereas the twisted nanofiber caused YAP confinement in the cytosol. Adapted with permission from American Chemical Society: Biomacromolecules; Arslan et al. [10] copyright (2017).

structural order (cross-β). Strategies to incorporate therapeutics into the peptide nanostructures using physical encapsulation [6,52,73,74] or chemical ligation approaches [4,7,75,76] have been extensively explored. Seminal work in drug targeting has revealed that 0D and 1D therapeutic carriers have distinctive biodistribution profile [26,77]. In regard to peptide assemblies, Yang et al. [78] have reported that 1D peptide nanofibers exhibit short circulating time upon intravenous injection, while Tanisaka et al. [79] have reported a 0D peptide nanovesicle that display a comparatively long circulation profile. Hence, the biodistribution profile of the peptide-based therapeutic carriers can potentially be adjusted through altering the morphology of peptide assemblies. Regarding targeting at the cell level, both 0D [4,6] and 1D [80] peptide nanostructures are preferentially taken up by antigen presentation cells (macrophages, dendritic cells, Figure 3a–b). Taking advantage of the immune cell targetability, these peptide nanostructures have been extensively explored as delivery carrier for vaccine epitopes [4,76,80] or immunomodulators [7,74]. Furthermore, the capability to trigger membrane translocation or endosome disruption is instrumental for transporting the therapeutic cargo into the cytosol for further processing and loading of the peptide epitopes into the MHC molecules. In this regard, β-sheet peptide assemblies have demonstrated good cell-membrane permeability, which can trigger endosomal escape, but the underlying mechanisms of endosomal escape remain unresolved [49,81]. Once the peptide assemblies reach the cytosol, their cellular fate is highly dependent on their supramolecular organization; the less-ordered structure (e.g. dynamic oligomers) will be directed to the ubiquitin proteasome pathway, whereas the more-ordered cross-β structures (e.g. 0D nanovesicle, 1D nanofiber) will be directed to the autophagy degradation pathway [82–84] (Figure 3b). In particular, because autophagy is an important cellular regulator of the immune responsiveness [85], the autophagy-engagement capability of these cross-β structures can be utilized in the development of oncotherapies [86] or immunotherapies [76,83,84].

Altering cell behavior by changing the morphology of 1D nanofibers

The self-assembly pathway control approach can also be used to optimize nanofiber applications in tissue engineering. Peptide nanofibers are an established building block of natural extracellular matrix (ECM)–mimicking matrix scaffolds that support three-dimensional tissue cultures of primary or stem cells [22]. These artificial viscoelastic fibrous mesh networks can be composed either through nonspecific internanofiber interactions [24] or specific nanofiber crosslinking [13]. Like fibrillar proteins present in the natural ECM, chirality [87–89] (Figure 3c) and helicity [10] (Figure 3d) of the peptide nanofibers are key modulators of cell behavior, such as adhesion, spreading, and proliferation. The chirality (right- or left-handed twist) of the nanofiber is generally altered by switching the chirality of the amino acids (D- vs L-amino acid) in the peptide [88,90], whereas the helicity (pitch and twist) is commonly altered by switching to different sequence [10]. However, altering the molecular chirality of amino acids can also change the cellular behavior [88]. The pathway control approach can be a more subtle alternative to adjust the chirality and helicity of the nanofibers. Besides, natural ECM transmits biological signals through cell binding sites, or functional motifs, to trigger cell growth and differentiation. Taking advantage of the modularity of peptide nanofibers [62], multiple functional motifs can be co-incorporated into such nanofibers [91]. The fiber morphology can alter the spatial arrangement of the functional motifs, which will directly affect their avidity and exposure to the targeted cell receptors [92]. By optimizing the nanofiber morphology via pathway control, we can directly modulate the interaction of functional motifs with target cells [93].

Coexistence of supramolecular products

One complication caused by self-assembling pathway complexity is the coexistence of assembled products within one supramolecular system [94]. For example, Liberta et al. [44] demonstrated the prevalent coexistence of polymorphic peptide nanofibers and oligomers within one supramolecular system. This system heterogeneity can alter the functional profiles of the peptide assemblies, for example,the drug-release profile will change if different 0D and 1D nanostructures coexist. Alternatively, mixtures of polymorphic peptide nanofibers for three-dimensional scaffolds for tissue engineering may cause differences in cell behavior. The composition of the supramolecular products must therefore be carefully characterized to give more predictable and repeatable results.

Conclusion and outlook

Self-assembling peptides form a prominent class of biomaterial for biomedical applications such as drug delivery and tissue engineering. To fully unleash the biomedical application potential of self-assembling peptides, several studies have explored the molecular organization of the final supramolecular peptide assemblies. This understanding of the molecular interaction at the atomic level within the assemblies has tremendously facilitated the search for a correlation between the primary peptide sequence and the supramolecular nanostructures. As a result, a few programmable peptide supramolecular systems have been developed and applied biomedically. Successful as it is, although, most of these engineering approaches require big molecular changes.

Increasing evidence suggests that peptide nanostructures are constructed through a multistep mechanism. This means that the outcome of the self-assembly process is critically influenced by their assembly pathway. Without making big changes in the peptide sequence, nanostructures of distinctive properties can be fabricated by influencing the assembly pathway. In this review, on the example of β-sheet assemblies, we have highlighted the strategies to derive 0D and 1D nanostructures through pathway selection. We have also discussed how this subtle engineering approach can benefit applications of self-assembling peptides for drug delivery and tissue engineering.

To further the applicability of the pathway control approach, there are a few challenges present ahead. First, the self-assembly process in general does not achieve full completion because of the activation energy barrier, which can lead to coexistence of side products alongside the main products. To avoid that such side products complicate the functionality of the peptide nanostructures, robust purification methods should be explored to select the desired products. Alternatively, the intrinsic system heterogeneity can also be explored as extra functionality. By deciphering the ratio of supramolecular products present, we can collectively use the assemblies to devise synergistic application. For instance, in tissue engineering applications, formation of 1D nanostructures can serve as infrastructural scaffolds, whereas coexistence of 0D nanostructures can serve as delivery systems for growth factors. At last, recent studies have explored the possibility of bridging dynamic covalent interactions to the noncovalent interactions in the build-up of 1D peptide nanostructures [95,96]. For example, the reversible disulfide exchange reaction has been explored as a complementary driver for the self-assembly of a 1D peptide nanostructures [95]. These complementary covalent and noncovalent interactions can be explored as stabilization strategy to generate biomaterials with enhanced longevity in the often-complex biological environment.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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* of special interest
** of outstanding interest

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