International Journal of Nanomedicine

Dovepress
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REVIEW

Molecular-Level Design Principles and Strategies of Peptide Self-Assembly Nanomaterials: From Sequence Engineering to Functional Applications

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Abstract: Peptide self-assembly has emerged as a pivotal strategy for constructing biomimetic functional materials, demonstrating extensive application potential in biomedicine and materials science owing to its superior biocompatibility, structural programmability, and dynamic tunability. Despite significant advances in this field, a comprehensive synthesis of molecular mechanisms and design methodologies remains lacking. This paper presents, for the first time, a systematic overview grounded in the hierarchical design of polypeptide molecules, elucidating key principles and strategies for engineering self-assembled peptide materials. This paper, for the first time, starts from the hierarchical design of polypeptide molecules and systematically sorts out the design principles and strategies of self-assembled peptide materials: from intramolecular factors such as amino acid sequence regulation, amphiphilic balance and chirality induction, to the hierarchical assembly mechanism driven by non-covalent interactions such as hydrogen bonds, hydrophobic interactions and π - π stacking. The influence of molecular engineering methods such as cofactor modification and co-assembly modification on the fine regulation of structure and function was further explored. Particular emphasis was placed on the methodological innovation of de novo design and bioinformatics aided design in the construction of self-assembled peptides, providing new ideas for achieving structural prediction and function-oriented design. This paper aims to construct a systematic strategy system from molecular basis to design framework, filling the gap in the summary of design methods in this field, and providing theoretical basis and design guidelines for the precise construction and functional expansion of polypeptide self-assembled materials.

Keywords: peptide-based self-assembly, peptide structure, co-assembly, conditional response, in situ assembly, application

Introduction

Self-assembly represents a ubiquitous phenomenon in nature, characterized by the spontaneous formation of ordered arrangements under thermodynamic conditions when molecular concentrations reach specific thresholds.[1] This molecular self-assembly process emerges from the equilibrium between intermolecular repulsive and attractive forces, ultimately stabilizing molecules in low-energy configurations.[2] Originating in the 1960s, the concept of molecular self-assembly describes the spontaneous organization of high-entropy systems into ordered micro/nanostructures through non-covalent interactions.[3] However, the scope of molecular self-assembly has significantly expanded, now encompassing assembly mechanisms involving covalent interactions.[3,4] This highly controllable and reproducible process enables the precise engineering of supramolecular structures with tailored physicochemical properties through the modulation of intermolecular forces, rendering it particularly valuable in materials science.[5] Peptides, as biohomologous molecules, serve as exemplary self-assembling building blocks owing to their superior biological activity, safety profile, and chemical versatility.[6] Self-assembled peptide nanostructures have garnered increasing attention due to their facile synthesis, structural tunability, and functional adaptability.

Received: 22 September 2025
Accepted: 10 December 2025
Published: 18 December 2025

Peptides, as a class of bioactive substances intermediate between amino acids and proteins, are small molecular compounds formed through covalent bonding of amino acids.[7] Self-assembly of peptides can be defined as the spontaneous formation of ordered structures utilizing short-chain amino acids as fundamental building blocks. This process represents a typical bottom-up approach for the fabrication of organic nanostructures characterized by complex and layered architectures.[8,9] Amino acids serve as the elementary units of peptides. The diverse combinations of 20 natural amino acids and various synthetic amino acids contribute to the extensive sequence variability of peptides.[10,11] Consequently, materials developed from peptides exhibit remarkable structural and functional diversity. The self-assembly mechanism of peptide molecules, akin to other molecular assemblies, primarily occurs through bottom-up organization driven by non-covalent interactions, enabling molecular chemical complementarity and structural compatibility.[12] These non-covalent interactions encompass hydrogen bonding, electrostatic interactions, hydrophobic effects, van der Waals forces, π-π stacking, and halogen bonding.[13] Peptide-based nanomaterials offer distinct advantages including facile molecular modification, co-assembly with other bioactive molecules/substances, and assembly design based on secondary structural elements. Firstly, diverse peptide sequences can be synthesized via solid-phase methods, allowing molecular-level modifications to produce peptide-based nanomaterials with tailored properties.[14–16] Secondly, specific structural assemblies can be achieved through rational utilization of peptide secondary structures.[17] Furthermore, peptide-based nanomaterials can be functionalized by incorporating functional molecules such as fluorescent markers into peptide nanostructures.[18] Beyond their inherent biocompatibility, biological activity, and biodegradability, peptide nanomaterials may also demonstrate exceptional thermal stability, environmental responsiveness, electrochemical properties, photosensitivity, and other characteristics, rendering them ideal biomaterial components.[19]

The self-assembly process orchestrates the unique stacking of peptide chains, facilitating the formation of higher-order nanostructures through either single-step or multi-step assembly mechanisms.[20,21] Leveraging the secondary structures of peptides, such as α-helices and β-sheets, along with the distinct characteristics of cyclic peptides and amphiphilic peptides, diverse nanostructures including nanofibers, nanotubes, vesicles, and hydrogels can be precisely engineered.[22] The amino acids, serving as the fundamental units of peptides, govern their physicochemical properties through variations in type, charge, size, and polarity, thereby enabling precise design and control of peptide structures.[23] Furthermore, the assembly process of peptides is influenced by environmental factors such as pH, temperature, ionic strength, and redox conditions.[23,24] By modulating these parameters according to the intrinsic properties of peptides, the formation of target structures can be effectively guided. In recent years, nanomaterials have experienced extensive development and application across diverse fields, including drug delivery, disease treatment, diagnostics, food science, environmental protection, and electronics.[25] Peptide-based nanomaterials, in particular, have garnered significant attention in bioengineering and biomedicine due to their exceptional biosafety, long-term stability, and diverse biological activities.[26] Additionally, the disassembly of peptide assemblies can be precisely regulated by enzymes, pH, and other factors, making them ideal candidates for drug delivery systems.[27] Beyond their biological applications, peptide nanomaterials exhibit remarkable thermal stability, semiconductor properties, piezoelectric effects, and optical characteristics, positioning them as promising materials in emerging electronic fields such as sensing, energy harvesting, energy storage, and electronic transmission.[28]

Since the advent of peptide self-assembly technology, a multitude of assembly methodologies have been developed. Currently, existing reviews on peptide-based self-assembled materials primarily focus on intermolecular interactions (eg, π–π stacking), assembly morphologies (eg, nanoparticles, nanofibers), and applications in drug delivery.[29–31] However, systematic design strategies and conceptual frameworks remain insufficiently summarized. This paper aims to explore the design strategies underlying polypeptide self-assembly, encompassing peptide primary structure, amino acid selection, secondary structure, the correlation between chemical properties and nano-morphology, as well as peptide modification and functionalization through co-assembly with diverse molecules. Furthermore, this paper highlights the applications of peptide-based self-assembling materials, spanning biomedical implementations and electrochemical material development. The primary objective of this work is to provide conceptual frameworks for the advancement and design of peptide nanomaterials.

Design Strategy of Peptide Nanomaterials

As fundamental biomolecules, peptides have been extensively investigated in the fabrication of bio-inspired materials. The structural configuration and biological functionality of peptides are of paramount importance, with amino acids serving as the foundational building blocks. The diversity of peptide activity is primarily determined by the specific types and sequential arrangements of amino acids. Three principal design strategies have been established for peptide-based self-assembly materials: (1) Structural and property-driven design, encompassing amino acid composition, secondary structure, peptide amphiphilicity, charge distribution, and chirality; (2) Functional modification of auxiliary groups or side chains; (3) Co-assembly with complementary functional components, including metal ions, bioactive small molecules, and biological macromolecules. Furthermore, the application of bioinformatics technologies has been demonstrated to significantly enhance the design efficiency of self-assembled peptides (Figure 1).

Peptide Framework and Properties

The biological functionality of peptides is intrinsically dependent on their amino acid sequence and spatial conformation. Consequently, the systematic regulation of amino acid composition and conformational arrangement must be meticulously considered during the development of peptide self-assembly materials. Amino acid selection is primarily governed by their chemical diversity, encompassing charged, polar, hydrophobic, and hydrophilic monomers. The distinct characteristics of their side chain groups enable different amino acids to exert aggregation effects through diverse intermolecular forces. Polar amino acids predominantly interact via hydrogen bonding and electrostatic interactions, whereas non-polar amino acids utilize hydrophobic interactions and π-π stacking to facilitate aggregation.[32] The classical secondary structures of peptides, namely α-helices and β-sheets, play a crucial role in the formation of specific nanostructures.[33] Furthermore, peptide self-assembly is typically driven by the amphiphilic properties inherent in monomer units, with the diversity of amino acid functional groups and the hydrogen bonding propensity of the amide backbone providing additional attractive and repulsive forces for self-assembly.[34] The hydrogen bonding network within the secondary structure of peptides significantly contributes to the structural integrity and stability of these assemblies. The precise chemical and structural design of peptides facilitates the replication of natural material characteristics and enables the development of novel functionalities. Thus, this chapter comprehensively summarizes the amino acid classification, secondary structure, and chemical properties of self-assembled peptides.

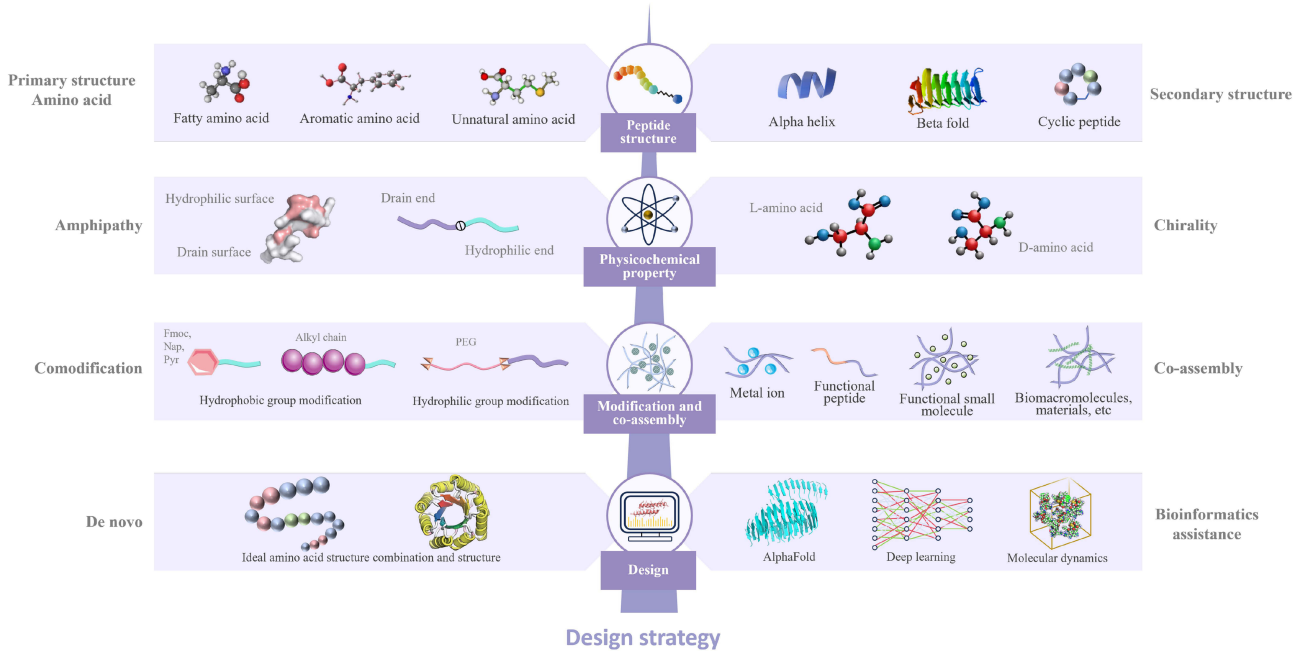

Figure 1 The main design strategy of peptide self-assembly materials.

https://doi.org/10.2147/IJN.S569237

Amino Acid Composition

The intrinsic properties of amino acids dictate the specific types of intermolecular forces governing peptide assembly, with amino acids being broadly classified into natural and non-natural categories. Given the predominantly hydrophobic environment characteristic of peptide assembly processes, aromatic amino acids within the natural amino acid group have garnered significant research attention. Subsequently, this discussion will systematically summarize the applications of various amino acid types in self-assembling peptide systems.

Natural Amino Acids

According to the assembly force, aliphatic amino acids (Ala, Val, Leu, Ile, Pro, Met) and aromatic residues (Trp, Tyr, Phe) in natural amino acids create a hydrophobic environment due to the presence of hydrophobic residues such as -CH_3 groups or benzene rings, which facilitate peptide assembly through π-π stacking interactions.[35] Another significant category comprises polar amino acids that promote assembly via electrostatic interactions (positively charged residues: Lys, Arg, His, negatively charged residues: Asp, Glu) and hydrogen bonding (uncharged residues: Ser, Thr, Asn, Gln). Furthermore, these polar amino acids can engage in hydrogen-bonding interactions through their -OH or -$CONH_2$ functional groups, thereby promoting peptide assembly formation.[23,35] Based on these fundamental principles, a series of peptides have been rationally designed. For instance, the Oleksii research team engineered a series of heptapeptides based on hydrophobic amino acids including Leu, His, Phe, and Ala. These peptides exhibit self-assembly properties, forming catalytic amyloid fibrils that effectively bind heme for chiral cyclopropanation reactions.[36] The DRF3 peptide, designed by Ruyue et al, features an alternating 1:1 ratio of hydrophilic and hydrophobic amino acids, with the hydrophilic components maintaining a 1:1 balance between basic and acidic residues, resulting in a neutral peptide. The hydrogel derived from this peptide's self-assembly demonstrates potential applications in anti-tumor therapy.[37] Furthermore, Glycine (Gly) reduces steric hindrance and enhances molecular flexibility due to its two hydrogen atoms, while Cysteine (Cys) provides modification sites through its disulfide bonds, expanding the functional possibilities of peptides.[38]

The amino acid sequence of peptides significantly influences their assembly formation capability, as well as the structural characteristics and biological activity of the resulting assemblies. Rational design of amino acid sequences is therefore crucial for developing peptide-based assembly materials. In a seminal study conducted by Lee et al, researchers systematically designed eight distinct peptide combinations based on Phe (F), Lys (K), and Glu (E) residues. By controlling the solvent environment and concentration, it can self-assemble into β-sheet nanoribbons or micelle-like aggregates (Figure 2a).[39] Furthermore, the proportional distribution of different amino acids significantly impacts peptide assembly characteristics. The Zhou team transformed the disordered structure of GL13K peptide into a β-sheet-rich structure by replacing lysine, leucine or isoleucine with the moderately hydrophobic alanine, and it self-assembled into twisted nanofibers.[40] However, peptides with single substitutions of Leucine or Isoleucine to Alanine maintained their disordered structures throughout the experimental observations, demonstrating no self-assembly behavior and exhibiting reduced antibacterial activity. In contrast, Meng et al employed more lipophilic amino acids, such as Glycine, resulting in structural transformations of peptide assemblies from vesicular morphologies to nanotube or nanoribbon formations.[41] Consequently, in the design of assembly-oriented peptides, it is essential to not only carefully select appropriate amino acid categories but also meticulously design the amino acid sequence and optimize the hydrophilic/hydrophobic amino acid ratio.

Aromatic Amino Acids

Tyrosine (Tyr) and Phenylalanine (Phe), serve as fundamental drivers for the self-assembly of ultrashort peptides, including dipeptides and minimal peptide sequences.[45,46] The assembly mechanism of these aromatic amino acids is primarily governed by hydrogen bonding and aromatic interactions, specifically π-π stacking phenomena.[22] Muhammad et al adopted the classic "sticker–spacer–sticker" motif to engineer the short-peptide derivative FFC5FF, which bears aromatic amino acids and a terminal amine. The synergistic π-driven interactions and hydrophobicity of the aromatic residues enable the peptide to self-assemble, under alkaline conditions, into a nanofibrillar hydrogel capable of encapsulating nitric oxide.[47] The Phe-Phe (FF) dipeptide represents a prototypical self-assembling short peptide that

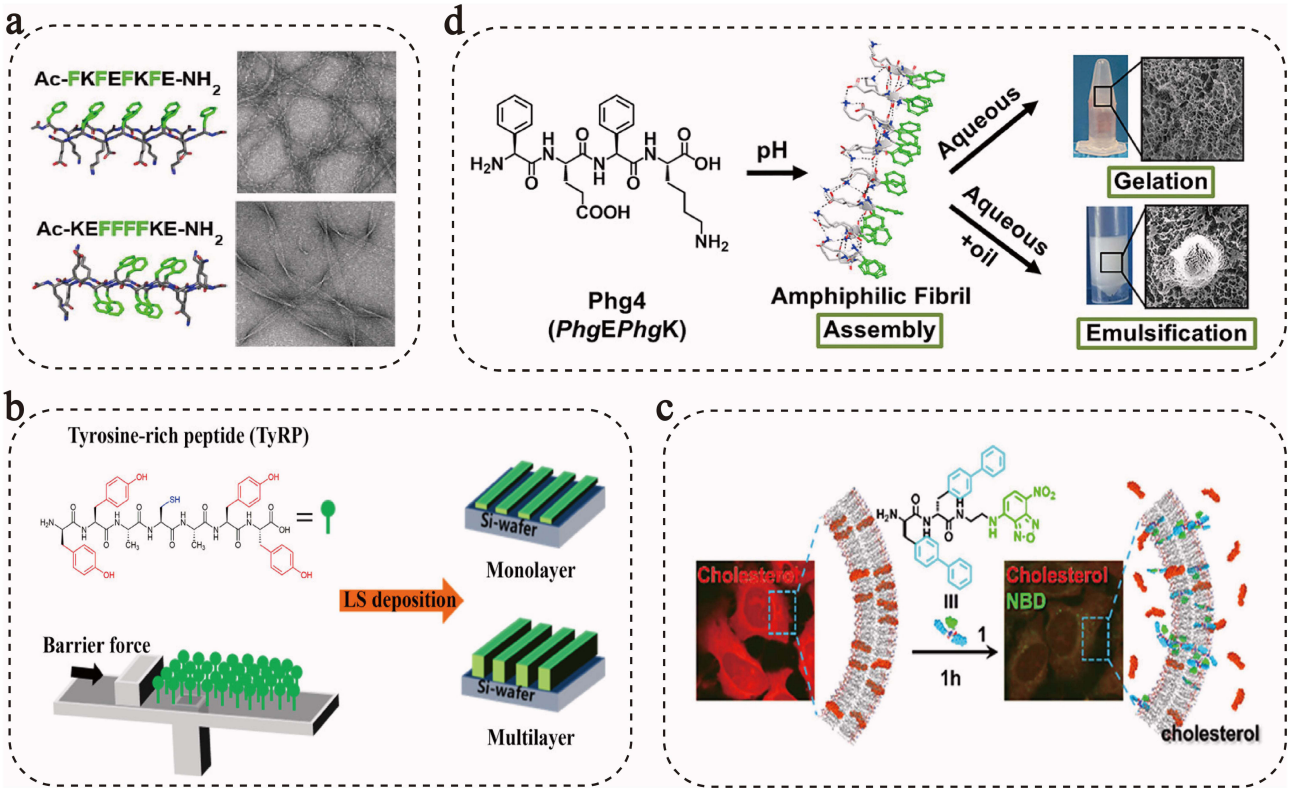

Figure 2 Design strategies of peptide-based self-assembly materials based on amino acids. (**a**) The overall hydrophobicity or charge of the peptide is the same, and the amino acid sequence pattern also affects the self-assembly tendency and morphology of the resulting material. Reproduced with permission from Ref.[39] Copyright 2013, American Chemical Society. (**b**) The tyramine-rich YYACAYY peptide sequence can form nanofilms with large size and controllable thickness. Reproduced with permission from Ref.[42] Copyright 2018, American Chemical Society. (**c**) The non-natural peptide bb-NBD assembly consumes cholesterol and inhibits cancer cells. Reproduced with permission from Ref.[43] Copyright 2024, American Chemical Society. (**d**) PhgEPhgK (Phg4), obtained by substituting flexible phenylalanine residue (F) with rigid phenylglycine (Phg), can be self-assembled into stable β-sheet nanofibers, which can be gelated and emulsified. Reproduced with permission from Ref.[44] Copyright 2020, American Chemical Society.

utilizes the π-π stacking interactions of its benzene rings to form stable nanostructures. At present, the self-assembly paradigm developed based on the FF dipeptide has garnered significant scientific attention, with numerous FF-derived self-assembly systems being systematically characterized.[48–50] Furthermore, research has demonstrated the feasibility of nanomaterial formation using single phenylalanine derivatives. Notably, Tan et al engineered a self-supporting super-hydrophobic material through the self-assembly of a single functionalized aromatic amino acid, Cbz-Phe(4F).[51] The fibrous architecture of this material's aggregates is stabilized through hydrogen bonding networks, while its isotropic growth is driven by hydrophobic interactions. In addition, Tyrosine is also applied in self-assembly, including the formation of hydrogels or films. Notably, Irina et al employed Langmuir-Blodgett and Langmuir-Schaefer deposition techniques to fabricate large-scale, thickness-controlled nanofilms from the tyramine-rich YYACAYY peptide sequence.[42] While aromatic amino acid-based assembly materials have been the subject of extensive research, they continue to present promising avenues for further development (Figure 2b).

Unnatural Amino Acid

In peptide design, the incorporation of non-natural amino acids serves to enhance structural rigidity, minimize protease recognition sites, introduce specialized functional groups, and optimize solubility.[52] Specifically, in the development of self-assembling peptide sequences, the strategic integration or substitution of non-natural amino acids can significantly augment assembly capabilities. Alpha-aminoisobutyric acid (Aib), a prominent non-natural amino acid, exhibits a rigid structure that constrains peptide backbone rotational freedom, promotes α-helix formation and stabilization, and effectively shields protease recognition sites.[53] Consequently, researchers have employed non-natural amino acids, particularly Aib, as glycine substitutes in peptides, thereby facilitating the spontaneous formation of well-organized

nanostructures.[54] Regarding other non-natural α -amino acids, Nilsson et al demonstrated that the incorporation of cyclohexylalanine, naphthalene alanine, and pentafluorophenylalanine into peptide sequences, when exceeding specific concentration thresholds, triggers the spontaneous formation of fibrillar structures.[55] Zhang et al developed peptide bb-NBD by substituting D-phenylalanine with the non-natural amino acid D-BiP, which significantly enhanced peptide assembly activity, resulting in micelle formation that effectively consumes cholesterol and inhibits cancer cell proliferation (Figure 2c).[43] Furthermore, the Jacek research group engineered a restricted analogue, PhgEPhgK (Phg4), by replacing the flexible phenylalanine residue (F) with the rigid phenylglycine (Phg).[44] This modification promoted the self-assembly of Phg4 into stable β-sheet structures. The distinctive structural advantages conferred by non-natural amino acids not only stabilize peptide conformations but also facilitate optimized assembly processes, offering valuable design principles for peptide engineering applications (Figure 2d).

Beyond their fundamental role as constituents of peptides and proteins, individual amino acids have demonstrated remarkable potential as autonomous self-assembling units. Notably, glycine (Gly) forms multiphase crystals and has the ability to generate electricity piezoelectric.[56] The fluorescence signal of L-lysine (L-Lys) self-assembled crystals is the strongest in water.[57] For a comprehensive analysis of amino acid-based nanomaterial design and assembly strategies, readers are directed to the seminal review by Wang et al, which provides an extensive synthesis of current research developments in this field.[58]

Peptide Structure

The intricate network of hydrogen bonding interactions among amino acid residues governs the formation of distinct secondary structural motifs in peptides. Through strategic design and manipulation of these secondary structures, peptides can be engineered to self-assemble into diverse nanostructural morphologies, including tubular, sheet-like, and spherical architectures. Among these, the α-helix and β-sheet configurations represent the most fundamental and extensively studied secondary structural elements. A comprehensive understanding of the correlation between secondary structure and peptide self-assembly mechanisms is crucial for advancing their applications across multiple scientific and technological domains.

Alpha Helix

The alpha helix is one of the most prevalent secondary structures in polypeptides, characterized by intramolecular hydrogen bonds along the peptide backbone.[59] This configuration results in a right-handed helical conformation with side chains extending outward. Such structural properties render it an ideal building block for self-assembling nanomaterials. However, short α-helical peptides often struggle to maintain their conformation in solution due to thermodynamic instability and require enhancement through sequence design or chemical modification.[60] In recent years, researchers have achieved controllable self-assembly of α-helical polypeptides using biomimetic strategies such as curly helices and collagen triple helices, as well as engineering approaches that involve introducing unnatural amino acids and crosslinking agents. These advancements have facilitated applications in biological materials, drug delivery systems, and tissue engineering.[22,46] The assembly mechanism of α-helical polypeptides primarily relies on the synergistic regulation of their structural characteristics and intermolecular interactions.[3] Key structural features include a rigid helical framework formed by amide hydrogen bonds within the main chain, alongside outwardly exposed side chains that participate in assembly via hydrophobic interactions, hydrogen bonding, electrostatic forces, or π-π stacking.[61] For example, the coiled helix, usually composed of 3–5 heptapeptides repeated, forms a polymer bundle through the regular arrangement of hydrophobic residues (such as alline) at the b, c, and f sites, and is further assembled laterally or longitudinally into nanofibers or hydrogels by hydrogen bonding or hydrophobic interaction.[22] Experiments have demonstrated that increasing the number of heptapeptide repeats (eg, from 3 to 5) can significantly enhance binding strength and reduce the thermodynamic dissociation constant from micromolar to picomolar levels. Furthermore, the orientation of the helix can be modulated through sequence design; for instance, the introduction of asparagine (N) residues at position a promotes parallel alignment, while end-chain cysteine (C) is cross-linked via disulfide bonds to stabilize the assembly orientation. In the design of collagen-like peptides, the repeated G-X-Y sequence, where X/Y is often proline/hydroxyproline, forms a triple helical structure by interchain hydrogen bonding.[62,63] The stability of this structure is

considerably influenced by both the length of the sequence and the type of residue present; for example, fluoroproline can elevate the melting point to 90°C.[62] Collagen trihelices are capable of forming fibrils through cross-stacking, with their assembly process relying on hydrogen bonding, hydrophobic interactions, and metal coordination (such as iron coordination mediated by bipyridine groups).[64,65]

Beta-Fold

Beta-sheet folding represents a pivotal secondary structure in peptide molecules, characterized by the parallel or antiparallel arrangement of peptide chains to form a lamellar architecture, stabilized through interchain hydrogen bonding.[66] A comprehensive hydrogen bond network is established between the amide groups of the peptide backbone, while the side chains extend perpendicularly to the peptide plane in an alternating fashion, thereby creating an amphiphilic interface.[22] This structural characteristic renders β-sheet peptides as the fundamental driving force in self-assembled nanomaterials, capable of forming diverse nanostructures including fibers, hydrogels, nanotubes, and vesicles through synergistic mechanisms of hydrophobic collapse, electrostatic interactions, and hydrogen bonding.[67,68] The assembly mechanism of β-sheet folding is governed by the cooperative interplay between the hydrogen bond-dominated rigid lamellar framework and the amphiphilic interface.[69] The stability and morphological diversity of β-sheet structures can be further enhanced through strategic alternation of hydrophilic and hydrophobic sequences or by incorporating non-natural amino acids, such as β-amino acid derivatives. For instance, conventional designs featuring alternately arranged hydrophobic and hydrophilic/charged residues constitute amphiphilic beta sheets that facilitate the assembly of nanostructures such as nanofibers.[19] The RADA16-I peptide, developed by Yokoi et al, forms a β-sheet core through the aggregation of hydrophobic alanine residues, while the charged aspartic acid and arginine residues are organized in the outer layer via electrostatic interactions, ultimately self-assembling into nanofibers.[70] The MAX1-7 peptide, designed by Schneider et al, adopts a β-hairpin structure induced by a central proline or flexible sequence, which promotes fiber formation in a salt solution through a hydrophobic valine outer layer.[71] Elisabeth's team engineered a β-peptide composed of residues derived from (1*R*, 2*S*)-2-aminocyclobutane-1-carboxylic acid, enabling self-assembly in specific media to produce nanofibers.[72] Benys et al enhanced the conformational stability and self-assembly propensity of peptides containing constrained β-amino acid residues by incorporating trans-(1*S*, 2*S*)-2-aminocyclopentanecarboxylic acid (*trans-ACPC*).[73]

Beta-sheet assemblies demonstrate significant potential in tissue engineering, drug delivery, and biosensing applications. Notably, the aromatic-free pentapeptide sequences IDIDI, DDIII, and DIIID have been shown to form stable and pH-responsive hydrogels.[33] The protonation of isoleucine residues facilitates charge recognition and hydrogen bonding, thereby driving β-sheet self-assembly and hydrogel formation. These pentapeptide-based self-assembled hydrogels exhibit tunable morphological and mechanical properties, along with self-healing and shear-thinning characteristics, making them promising candidates for tissue engineering, injectable delivery carriers, and 3D printing applications (Figure 3a). Furthermore, the pentapeptide Asn-Gly-Ile-Trp-Tyr-NH_2 (NGIWY-amide), isolated from the sea cucumber Apostichopus japonicus, forms rigid hydrogels with a high β-sheet content in aqueous solutions, serving as effective carriers for localized drug delivery.[74]

Cyclic Peptide

The experimental demonstration of cyclic peptide nanotubes as transmembrane ion channels represents a pivotal milestone in the field of self-assembling peptides.[76] Ghadiri et al pioneered the design of a series of hetero-chiral cyclic peptides that stack to form hollow cylindrical nanostructures capable of spanning membrane channels.[77] Through rational design of the amino acid composition, cyclic peptide molecules can self-assemble via stacking interactions to form stable α-helical or β-sheet structures.[78] These cyclic peptide molecules assemble into open nanotubes through stacking, with the amino acid side chains positioned on the exterior of the tube and the peptide backbone located on the interior.[79] The outer surface properties and inner diameter of these nanotubes can be precisely controlled by judicious selection of amino acid side chains and the number of amino acids incorporated into the cyclic peptides.[80] Strategic design enables the cyclopeptide assemblies to achieve stable conformations and diverse functionalities. Notably, the cyclic octapeptide Lanreotide (D-Nalphtyl-Acyd-WKVMT-$CONH_2$), a growth hormone inhibitor, can self-assemble into viral capsid-like

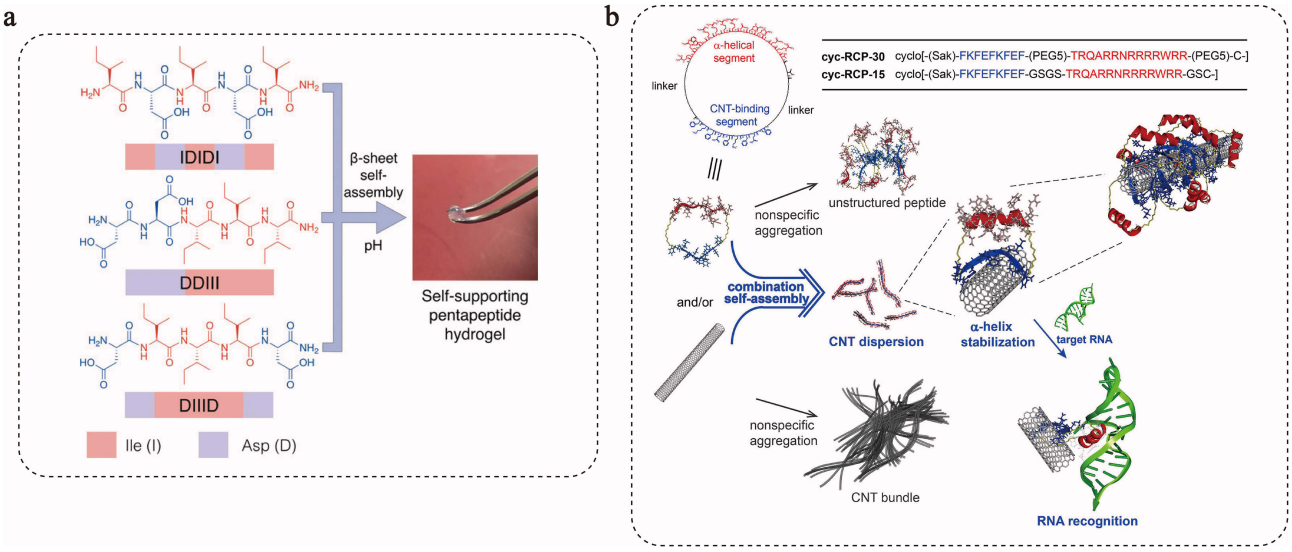

Figure 3 Design strategies of peptide-based self-assembly materials based on secondary structure of peptides. (**a**) Three pentapeptide sequences without aromatic groups are induced by a change in pH value to form a robust β-sheet hydrogel. Reproduced with permission from Ref.[33] Copyright 2018, Wiley-VCH GmbH. (**b**) Peptides and CNT to form a stable α -helical structure and can specifically recognize target RRE RNA. Reproduced with permission from Ref.[75] Copyright 2013, American Chemical Society.

nanotubes.[81] Additionally, Jeong et al utilized a hybrid cyclic peptide to construct a stable α-helical carbon nanotube structure (Figure 3b).[75]

Amphipath

Amphiphilic peptides represent a prominent category of self-assembling peptides whose properties have been extensively investigated. These peptides are functional molecules that achieve controlled self-assembly through the strategic alternation of hydrophobic and hydrophilic amino acids.[82] By arranging hydrophobic and hydrophilic residues in an alternating pattern, amphiphilic peptides spontaneously assemble into well-ordered nanostructures, including nanofibers, micelles, and hydrogels, in aqueous solutions via non-covalent interactions such as hydrophobic effects, hydrogen bonding, and electrostatic attractions.[83] For instance, the elastin-like peptide (ELP), an amphiphilic peptide, features a repeating VPGVG motif as its hydrophobic domain. This peptide is utilized in dynamic stents and controlled drug release systems due to its temperature-responsive phase transition behavior, existing in a soluble state at lower temperatures and transitioning to a β-helix condensed phase at elevated temperatures.[84] Enhanced hydrophobicity in peptides has been shown to promote self-assembly.[85] The amphiphilic nature of peptide molecules can be precisely modulated by rationally designing the sequence, quantity, and ratio of hydrophilic to hydrophobic amino acids within the peptide chain.[86] Surfactant-like peptides and lipid-like peptides represent two prominent categories of self-assembling peptides. The surfactant-like peptide structure incorporates a lipophilic tail composed of charged hydrophilic groups and hydrophobic amino acids such as alanine (A), valine (V), and leucine (L) through the C-terminus, while maintaining an uncharged N-terminus.[78] A representative example, Ala_9-Arg (A9R), demonstrates the ability to self-assemble into a β-sheet fiber structure at critical aggregation concentrations.[87] These fibrous structures not only facilitate the formation of hydrogels but also stabilize oil-in-water emulsions, exhibiting significant selective antibacterial activity against gram-negative pathogens such as Pseudomonas aeruginosa. Another notable peptide, Arg_3-Leu_{12} (R_3L_{12}), forms peptide nanotube networks at pH values of 9 and below.[88] Regarding lipid-like peptides, their self-assembly necessitates the presence of charged amino acids on one terminus and highly hydrophobic amino acids on the opposite terminus.[12] Several lipid-like peptides, including ac-A6K-$CONH_2$, KA6-$CONH_2$, ac-A6D-COOH, and DA6-COOH, demonstrate potential as intestinal permeability enhancers, suggesting promising applications in the oral delivery of diagnostic and therapeutic molecules.[89]

To increase the hydrophobicity of a peptide, in addition to the introduction of a hydrophobic amino acid into the peptide sequence. A simple strategy is to attach a hydrophobic group (eg C12-C16 alkyl chain) to one end of the peptide

chain so that the resulting peptide derivative behaves similar to the formation of amphiphiles by surfactants or liposomes.[90] The peptides IKPEAP and IKPEAPGE are the first six and eight amino acids, respectively, from the peptide sequence of the gastrointestinal peptide hormone PYY3-36.[43] After the N-terminal of the two peptides is connected with palmitoyl C16, the nanostructure formed by self-assembly of lipidized PYY3-36 fragments can be adjusted by controlling pH value or concentration (Figure 4a). In addition to the aforementioned categories, modular sequences are frequently employed in the design of amphiphilic peptides.[22,23] The design typically comprises four distinct modules: Module 1 consists of a hydrophobic tail, formed by alkyl chains or non-polar amino acids such as valine and alanine, which drives hydrophobic collapse to establish the assembly core; Module 2 incorporates sequences capable of forming stable secondary structures, including β-sheets or α-helices (eg, polylysine), which function as connecting regions and facilitate fiber extension through hydrogen bonding; Module 3 includes charged residues (such as glutamate and lysine) that regulate interface curvature and solubility; Module 4 features optional bioactive epitopes (eg, RGD sequence) that confer cell adhesion, targeting, and other biological functionalities. A notable example is the peptide amphiphiles (PA) developed by Hartgerink's team in 2001, which utilized a four-domain design to successfully mimic bone tissue complexes.[9] This was achieved through the synergistic interaction of a hydrophobic alkyl chain with a β-sheet peptide to form a fibrous scaffold, thereby inducing hydroxyapatite deposition. The rational design of amphiphilic peptide assemblies holds significant potential for applications in tissue engineering and precision medicine, warranting further development. Readers with an interest in amphiphilic peptide self-assembly are encouraged to explore additional literature, such as the comprehensive review authored by zhao et al.[91]

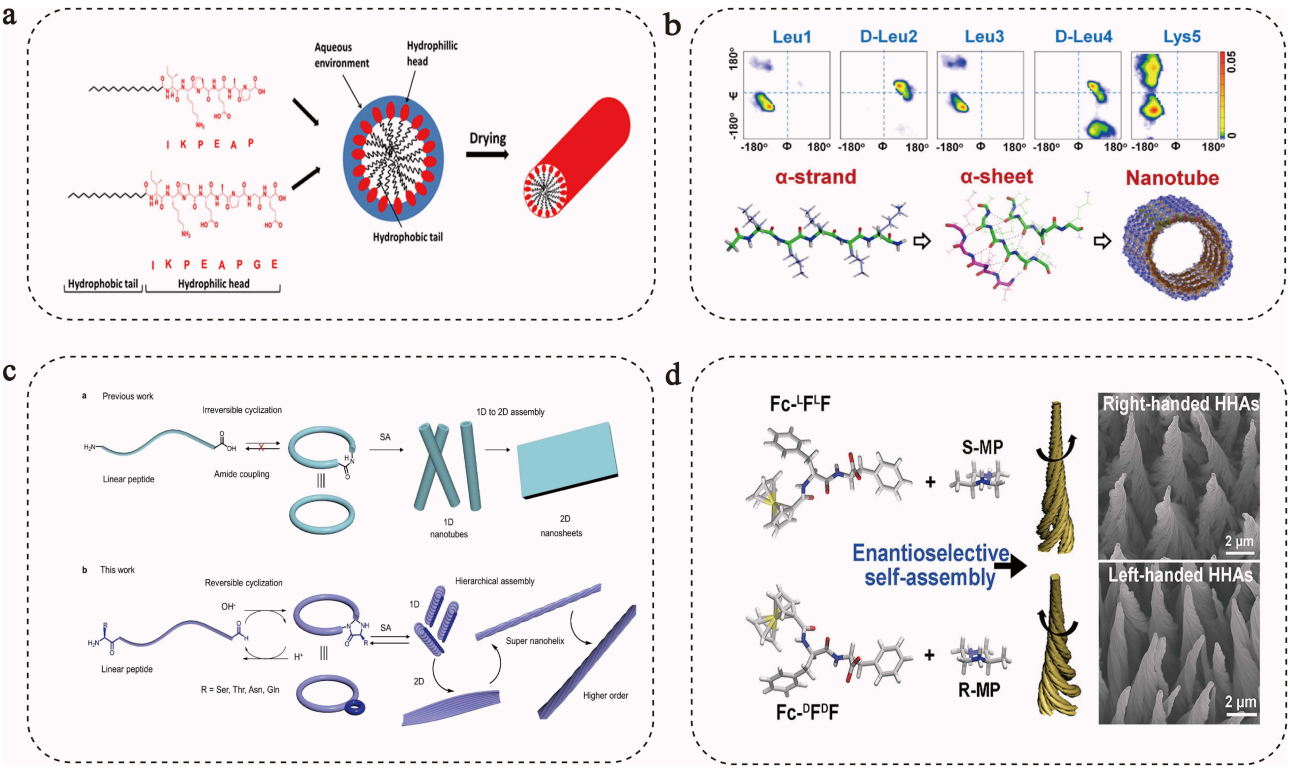

Figure 4 Design strategies of peptide-based assembly materials based on amphipath and chirality of peptides. (**a**) The lipids C16IKPEAP and C16IKPEAPGE form spherical micelles in aqueous solution and form β-sheet nanofibril when dried. Reproduced with permission from Ref.[43] Copyright 2024, American Chemical Society. (**b**) The two heterochiral peptides with different configurations were folded into α-sheet structure and easily piled into tubular structure in oligomer simulation. Reproduced with permission from Ref.[92] Copyright 2022, American Chemical Society. (**c**) Natural chiral inversion, chain tautomerism and layered assembly were studied by using asymmetric cyclic peptides constructed by dynamic covalent chemistry. The introduction of chirality in the asymmetric cyclic peptides of 4-imidazolidinone ring promotes the formation of winding nanostructures. Reproduced with permission from Ref.[93] Copyright 2023, Wile-VCH GmbH. (**d**) By changing the chirality and enantioselective interactions, the phase behavior, rotation and chirality of the self-assembled HHA can be precisely controlled. Reproduced with permission from Ref.[94] Copyright 2021, American Chemical Society.

https://doi.org/10.2147/IJN.S569237

Chirality

Peptide chirality represents a fundamental characteristic in peptide self-assembly, with its study originating from the "wavy" β-sheet structure hypothesis proposed by Pauling and Corey in 1953.[95] They postulated that the alternating arrangement of D-peptides and L-peptides could enhance assembly stability through the nested hydrophobic interactions of side chains, a hypothesis subsequently validated by experimental studies. For instance, Zhou et al revealed that the homochiral peptide Ac-LLLLK-NH_2 forms twisted nanofibrils, while the designed chiral amphiphilic peptides Ac-LDLLDLK-NH_2 and Ac-DLLDLLDK-NH_2, featuring alternating L-type and D-type amino acids, assemble into highly ordered wide nanotubes and single-layer helical ribbons (Figure 4b).[92]

Chiral peptides exhibit remarkable tunability in mechanical properties and structural diversity. For instance, the D/L enantiomers of β2-microglobulin K3 form independent fibrils without cross-reactivity, whereas the D/L mixture of L4K8L4 undergoes a complete assembly pathway transformation, resulting in non-fibrous spherical aggregates.[96,97] Chongyang et al introduced chiral peptides derived from the asymmetric 4-imidazolidinone ring, resulting in D- and L-cyclic peptides that facilitate the transition from one-dimensional to two-dimensional assembly.[93] Subsequent self-assembly leads to the formation of a higher-order coil in a left-handed configuration, thereby demonstrating chiral-induced self-assembly (Figure 4c). Hai et al discovered that Ac-^{L}I4^{L}K^{L}K-NH_2 and Ac-^{L}I4 ^{D}K^{D}K-NH_2 self-assemble into thin, twisted left-handed nanofibrils.[98] While Ac-^{L}I4 ^{L}K^{D}K-NH_2 forms thick left-handed nanofibrils through the stacking of thin fibrils, and Ac-^{L}I4 ^{D}K^{L}K-NH_2 predominantly assembles into wide nanotubes. Their findings revealed that even subtle chirality alterations in just two C-terminal lysine residues significantly influenced the self-assembly morphology of these peptides. Additionally, studies utilizing Fc-^{L}F^{L}F and Fc-^{D}F^{D}F peptides investigated the geometric frustration induced by chiral interactions (Figure 4d).[94] As well as the transition of self-assembled peptide membranes from achiral spherulite structures to chiral helical hierarchical assemblies (HHA), offering valuable insights for the design of highly ordered functional chiral materials. Chiral design strategies primarily focus on three aspects: enantiomer ratio modulation, side chain engineering, and sequence optimization. By adjusting the D/L ratio or selecting specific residues, interactions can be precisely directed to enhance the mechanical properties of mixed enantiomer systems. For instance, the incorporation of valine in the MAX peptide hydrophobic core doubled the mixed enantiomer modulus, while the introduction of arginine's guanidinium group, which forms hydrogen bonds, increased the modulus by 11-fold.[99] In contrast, isoleucine exhibits a limited contribution to stiffness enhancement due to its low side chain nesting energy, underscoring the critical importance of judicious side chain selection in chiral peptide design.

Comodification

In the design of self-assembled peptides, the incorporation of hydrophobic moieties, particularly aromatic groups, substantially enhances their functional properties and modulates their self-assembly behavior.[100,101] These aromatic groups facilitate peptide aggregation in aqueous media through hydrophobic interactions, while simultaneously stabilizing the assembled structures via π-π stacking of aromatic rings, thereby conferring mechanical strength and thermal stability to the material.[58] Conversely, the introduction of polyethylene glycol (PEG) can augment hydrophilicity, thereby improving both the aqueous solubility and biocompatibility of the peptide assemblies.[102]

The conjugation of aromatic moieties with short peptides significantly augments their self-assembly induction capability through π-π stacking interactions, reducing reliance on long-chain amino acids and enhancing peptide hydrophobicity. Prominent aromatic groups employed in this context include fluorenylmethoxycarbonyl (Fmoc), naphthol (Nap), pyridinyl (Pyr), and phenylboronic acid. Among these, Fmoc-FF represents the most extensively studied Fmoc-modified dipeptide, which undergoes self-assembly through hydrogen bonding and π-stacking interactions to form β-sheet structures at neutral pH.[22] Notably, the morphology of these assemblies can be modulated to form rods, hydrogels, and other nanostructures through pH adjustment. Numerous studies have substantiated that the introduction of Fmoc groups substantially enhances the self-assembly propensity of peptides. Santu Bera et al modified glycine, proline and their translated product 4-hydroxyproline by Fmoc to form a series of single triplet motifs, which showed a natural collagen-helical structure and further formed hydrogels.[103] Min-Rui et al constructed a stable hydrogel system by co-assembling Fmoc-FRGDF peptide and fucoidan to deliver and control the release of hydrophobic bioactive flavonoid hesperidin (Figure 5a).[104] Fmoc-modified single amino acids Fmoc-L and Fmoc-W have also been designed

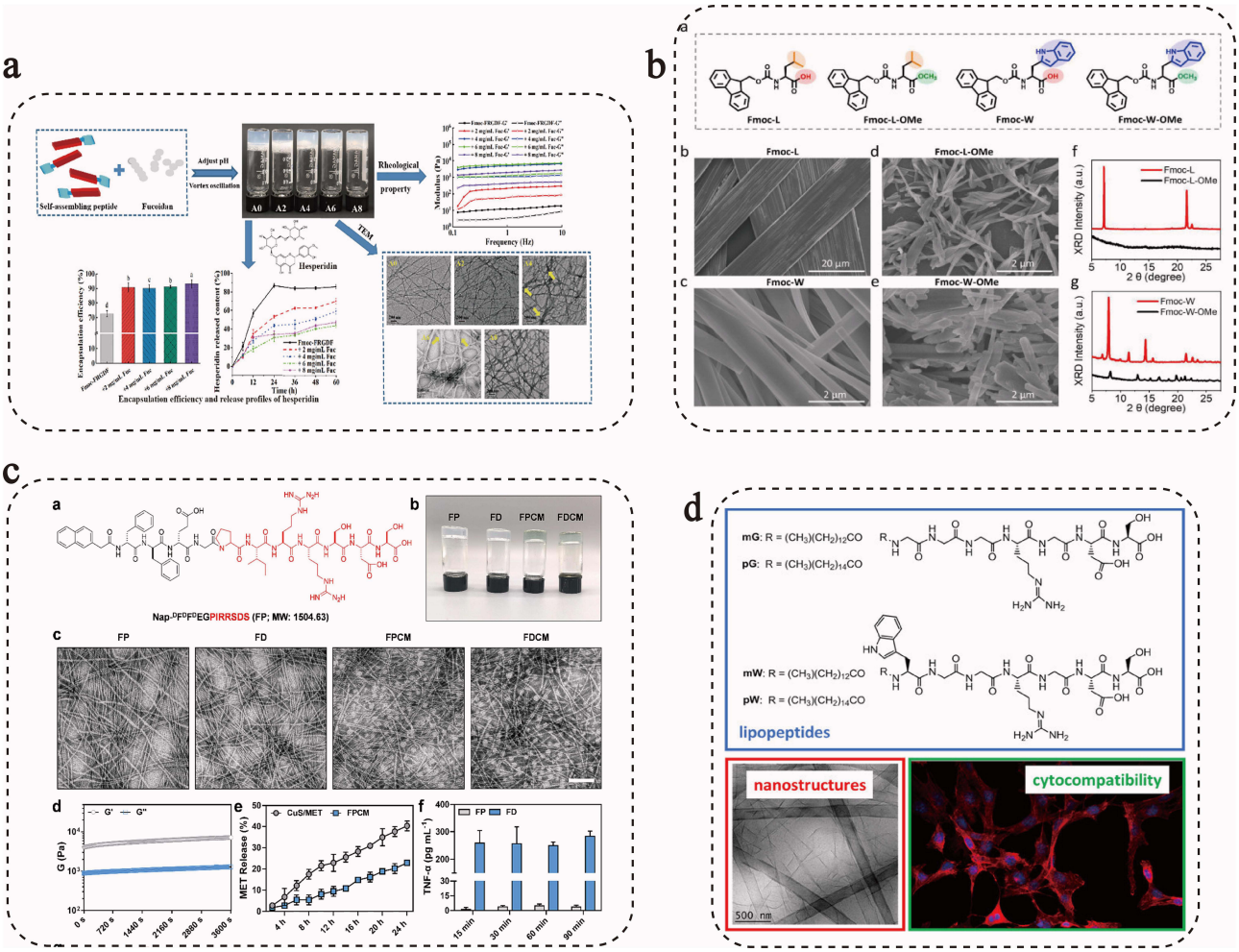

Figure 5 Design strategy of polypeptide-based self-assembly materials based on cogroup modification. (**a**) Fmoc-FRGDF polypeptide and fucoidan polysaccharide were assembled together to construct a stable hydrogel system, which could be used to deliver and control the release of hydrophobic bioactive flavonoid hesperidin. Reproduced with permission from Ref.[104] Copyright 2023, Elsevier. (**b**) Chemical structure and assembly morphological diagrams of Fmoc-L, Fmoc-L-OMe, Fmoc-W and Fmoc-W-OMe. Reproduced with permission from Ref.[105] Copyright 2022, Elsevier. (**c**) Polypeptide Nap-DFDFDEGPIRRSDS can be assembled to form a hydrogel with TNF-α binding ability. The integration of metformin's copper sulfide nanoparticles (CuS/MET NPs) into the hydrogel can enhance the antisynovitis and cartilage repair properties of the hydrogel. Reproduced with permission from Ref.[106] Copyright 2023, Elsevier. (**d**) All four lipopeptides form extended β-folded nanostructures at sufficiently high concentrations and exhibit good cytotoxicity at low concentrations. Reproduced with permission from Ref.[107] Copyright 2022, The Authors. Published by American Chemical Society.

for self-assembly, which exhibit high current response and fluorescence signal, and can be further assembled into bionic semiconductor materials (Figure 5b).[105]

In addition to Fmoc, Nap and Pyr groups are also commonly used in the modification of self-assembling peptides. Yu et al designed a nanoscale antimicrobial self-assembly short peptide Nap*(Nap-^{D}Nal-Nal-Dab-Dab-NH_2),[100] which can spontaneously assemble into nanofibers and has broad spectrum antibacterial action and excellent biocompatibility. Similarly, the Nap-^{D}F^{D}F^{D}EGPIRRSDS peptide, which forms an injectable hydrogel, also binds to the inflammatory factor TNF-α (Figure 5c).[106] FF, the most common dipeptide motif, can be modified with Nap or Pyr to show a fibrous form. However, Nap-FF is formed by antiparallel stacking, and Py-FF forms parallel stacking aggregates due to the strong π-stacking interaction of pyrene groups.[108] Mustafa's team modified the N-terminal of the peptide LLLKKK or PPPKKK with Pyr.[101] Pyr-LLLKKK self-assembled into beta fibulae at specific pH, and Pyr-PPPKKK formed spherical aggregates with random coil concentrations under acidic and alkaline conditions.

Furthermore, alkyl chain modification represents a robust strategy for enhancing the hydrophobic characteristics of peptides. Elisabetta et al successfully conjugated a C_{14} alkyl chain with peptide sequences WGGRGDS and GGGRGDS, demonstrating that the resulting C_{14}-WGGRGDS hydrogels exhibited a unique coexistence of helical twisted ribbons and

https://doi.org/10.2147/IJN.S569237

nanotubular structures.[107] These hydrogel systems demonstrated significant potential as cellular scaffolds for both fibroblasts and myoblasts, while simultaneously enhancing cytocompatibility (Figure 5d). Notably, alkyl chain modification of antimicrobial peptides has been shown to enhance their antibacterial efficacy while concurrently reducing cytotoxicity. For example, the modification of the short peptide KKKWW with alkyl chains at two sites.[109]

The inherent hydrophobicity of peptides often results in compromised solubility and elevated immunogenicity risks, posing significant challenges for their pharmaceutical development.[110] Consequently, the integration of polyethylene glycol (PEG) presents a promising strategy to enhance peptide material performance and broaden their application spectrum through its distinctive hydrophilic properties and biocompatibility.[111] The extended hydrophilic chains of PEG can form "stealth" shells that effectively mask hydrophobic domains and potential epitopes of peptides, thereby substantially mitigating immunogenicity and minimizing non-specific protein adsorption.[112] Furthermore, PEG incorporation facilitates the optimization of amphiphilic balance in peptide molecules, driving their self-assembly into diverse nanostructures such as micelles and vesicles.[111] A notable example is the work by Xin et al, who successfully synthesized PEG-peptide conjugates through DIC-assisted acid-amine condensation chemistry, utilizing PEG400, PEG700, and PEG1000 at the N-terminus of peptides.[102] In these constructs, the PEG chains are strategically positioned on the surface of peptide assembly sheets, creating accessible sites for functional small molecule attachment, thus offering significant potential for further development.

Coassembly

In the process of peptide self-assembly, intricate nanostructures are constructed through non-covalent interactions or covalent coupling between peptides and other functional molecules, including metal ions and functional small molecules. This strategy facilitates functional integration and performance optimization by leveraging the complementary properties of these molecular components. For instance, metal ions enhance material stability and catalytic activity through coordination bonds, while functional peptides confer biological activities such as anticancer and antibacterial properties. Additionally, functional molecules like porphyrins introduce therapeutic capabilities, including photothermal and photodynamic functions. Furthermore, co-assembly enables the regulation of nanostructure morphology, enhances hydrophobic drug loading capacity, and achieves controlled release through environmentally responsive molecules, all while preserving the biocompatibility inherent to natural peptides. Co-assembly also expands the conformational space of supramolecular assemblies in terms of structural and functional complexity, making it a highly effective approach in the design of self-assembled peptides.

Metal Ion

The investigation of co-assembled nanomaterials comprising metal ions and peptides stems from the biomimetic design of natural metalloproteins. Through the coordination of residues such as cysteine and histidine with metal ions, peptide conformational transformations are induced, leading to the formation of dynamic nanostructures.[22] These materials exhibit metal-specific responsiveness, environmental regulation capabilities, and functional programmability, making them suitable for applications in high-sensitivity detection, environmental remediation (eg, heavy metal adsorption), and antimicrobial therapy.[113,114] From an amino acid perspective, the chelation of metal ions can be categorized into peptides without coordinating side chains (eg, alanine or phenylalanine) and those with coordinating side chains (eg, histidine or cysteine). Peptides lacking coordinating side chains can chelate metal ions through amino or carboxylate terminals, or via terminal amino groups and adjacent carbonyl groups.[115] Amino acids possessing coordinating side chains are frequently employed in the fabrication of metal ion co-assemblies. For instance, Nyla et al synthesized colloidal nanomixtures of silver peptides through the photochemical reduction of the amphiphilic tripeptide IFH and silver metal, facilitated by mild ultraviolet light irradiation.[116] These hydrogels demonstrated the ability to modulate the Ag+ release profile, thereby exhibiting potent antibacterial and anti-biofilm biological activities (Figure 6a). Similarly, other researchers have successfully assembled copper nanoclusters with the FFC tripeptide and copper ions, resulting in nanostructures that exhibit remarkable stability and intense fluorescence.[117] These properties render them suitable for the detection of ascorbic acid levels, offering valuable insights for the development of novel sensing platforms based on nanoclusters and ascorbic acid detection (Figure 6b). Among them, the short peptide-silver nanocomposites constructed by using self-

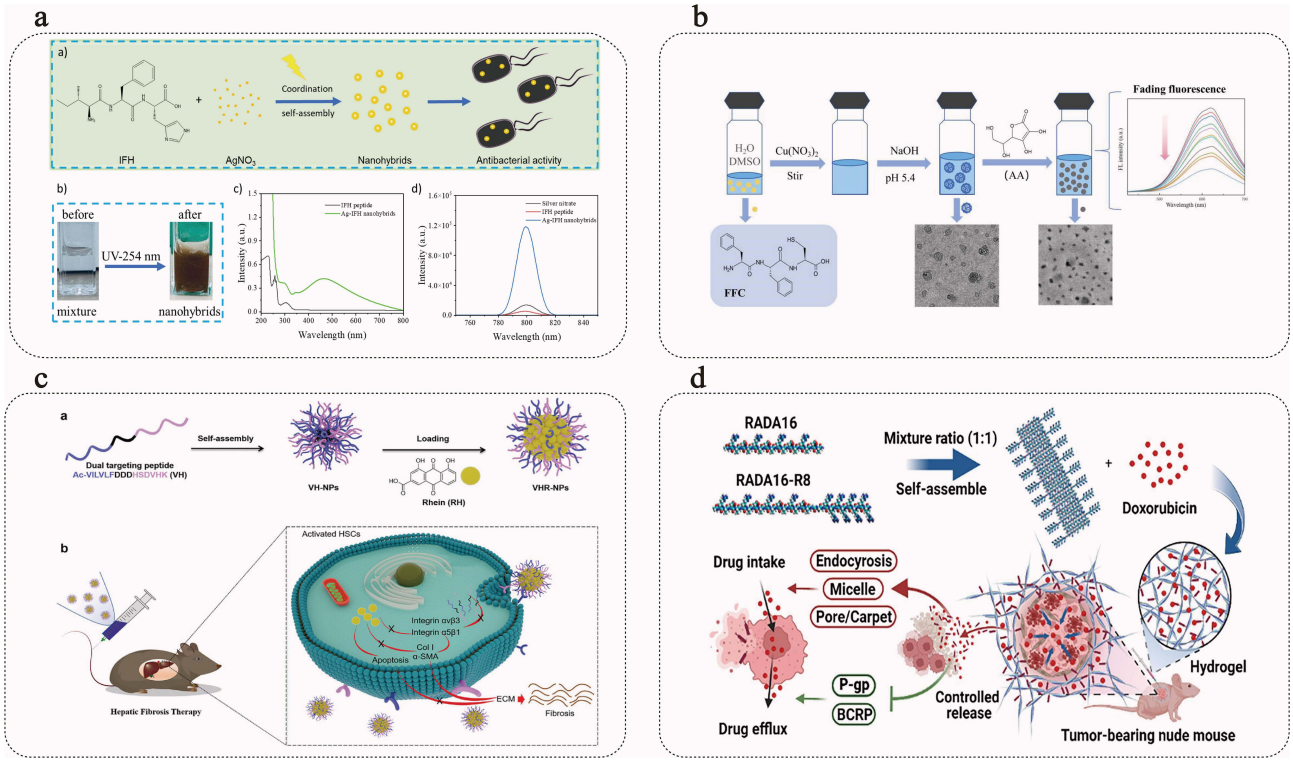

Figure 6 Co-assembly design strategy for metal ions, multifunctional peptides and assembly peptide sequences. (**a**) Amphiphilic tripeptide IFH, as a reducing agent and terminating agent of silver metal, was formed by photochemical reduction method with the mild assistance of ultraviolet light (254 nm). Reproduced with permission from Ref.[116] Copyright 2024, The Authors. (**b**) FFC tripeptides and copper ions are assembled into copper nanoclusters, which form a stable nanostructure with strong fluorescence and can be used to detect ascorbic acid content. Reproduced with permission from Ref.[117] Copyright 2024, The Authors. (**c**) Reasonably designed self-assembly peptide Ac-VILVLFDDDHSDVHK (VH) can double target integrins α5β1 and αvβ3. After self-assembly, the drug RH can be encapsulated, and the resulting VHR-NPs has enhanced anti-fibrotic effect and good biocompatibility. Reproduced with permission from Ref.[120] Copyright 2024, Wiley-VCH GmbH. (**d**) RADA16 (RR) self-assembled peptide modified by the cell-penetrating peptide octaarnine (R8) can be used to form nanofiber hydrogels, which can be used as anticancer drug carriers for the treatment of multidrug-resistant cancers. Reproduced with permission from Ref.[121] Copyright 2024, Elsevier.

assembled short peptides as green reducing agents, structural templates and stable carriers, in combination with silver metal, have become a new type of antibacterial platform for treating drug-resistant bacterial infections. Mussarat et al have elaborated on this in detail in the literature.[118] Furthermore, the incorporation of metal ions can significantly influence the morphological characteristics of the assembly. Abul-Haija et al utilized copper ions to mediate the cooperative co-assembly of two tripeptides (Ph-Ph-Asp and Gly-His-Lys) into hydrogels.[119] In the absence of copper ions, only nanofibers were formed. However, upon the addition of copper ions, the researchers observed the transformation into co-assembled nanoribbons and nanofibers, culminating in the formation of hydrogels.

Functional Peptide

Functional peptides are integrated with self-assembled motifs through covalent bonding or covalent conjugation to construct multifunctional nanostructures. The core principle of this design is to preserve the secondary structure of the functional peptide (eg, α-helix, β-sheet) to ensure biological activity while maintaining the intermolecular interactions of the assembled peptide.[122] This approach endows the assembly with precise targeting capabilities and specific biological activities, demonstrating significant potential in tumor-targeted therapy, molecular imaging, disease treatment, and other related fields.[123]

Targeting Peptide

The ability to specifically bind to target sites is a crucial characteristic of an ideal drug carrier. The integration of targeting sequences with self-assembled motifs has been extensively utilized in drug delivery systems, significantly enhancing the drug uptake rate due to the targeting function.[124] For instance, the self-assembling peptide Ac-

VILVLFDDDHSDVHK (VH), which exhibits dual integrin-binding modalities for α5β1 and αvβ3, can assemble into highly ordered nanofibers or nanoparticles (VH-NPs).[120] These VH-NPs can encapsulate rhein through non-covalent interactions, demonstrating the potential of supramolecular peptide nanostructures for enhanced liver delivery and anti-fibrosis therapy (Figure 6c). Additionally, the TPE-GFFYGRGDK-N_3 sequence, designed by Chen et al, targets tumor surfaces via the RGD motif.[125] This sequence induces nanofiber formation on the tumor surface, effectively inhibiting tumor cell migration and invasion.

Cell Penetrating Peptide

Cell-penetrating peptides (CPPs), capable of directly traversing the cellular membrane, exert their therapeutic effects in cancer treatment primarily through endocytosis and direct membrane penetration.[126] For instance, octaarginine (RRRRRRRR, R8) has been extensively employed in the construction of liposomes and peptide-drug conjugates for anticancer applications. A novel injectable formulation utilizing R8-modified RADA16 self-assembling peptide nanofiber hydrogel has been developed as an advanced drug delivery system for multidrug-resistant cancer therapy (Figure 6d).[121] Furthermore, Zhu et al integrated the structure-activity relationship of antimicrobial peptides with self-assembly principles, employing a modular design strategy that combines the self-assembly core, hydrophobic motif, and cell-penetrating unit to develop multifunctional self-assembling nanopeptides, such as F3FT, for combating intracellular bacterial infections.[127]

Anticancer Peptide

Anticancer peptides (ACPs) exhibit significant therapeutic potential by inhibiting tumor cell proliferation and migration, as well as suppressing tumor angiogenesis, while demonstrating reduced propensity for inducing cellular drug resistance.[128] The RADA-KLA peptide scaffold, engineered with the antitumor motif KLA (KLAKLAKKLAKLAKLAK) as its self-assembly core, forms nanofiber hydrogels that effectively induce cellular apoptosis and inhibit hepatocellular carcinoma cell adhesion and migration.[129] R. Aronson et al developed a novel class of peptide-lipid particles, liposomes (LPs), by leveraging the membrane-specific interactions of ACPs. These LPs demonstrate efficient encapsulation of oncolytic ACPs while maintaining stability during prolonged storage.[130]

Antimicrobial Peptide

Antimicrobial peptides (AMPs) have been shown to have strong cytotoxic and anti-inflammatory activity against multi-drug resistant bacteria.[131] Feng et al conjugated the self-assembling peptide RADA16 with antimicrobial peptides to develop RA-AMPs.[132] Additionally, a PNIPAM hydrogel containing the MGF E peptide was incorporated into another PNIPAM hydrogel, resulting in a multifunctional hydrogel that serves as both an antibacterial agent and a wound healing carrier. In order to give antimicrobial peptides self-assembly, cell selectivity and other functions, some researchers introduced FA into antimicrobial peptides and designed $K_3(FA)_4K_3$ and $K_6(FA)_4$ sequences according to the core motif KLVFFA in Aβ1-42.[133] The peptide based nanofibril was constructed by self-assembly. It was found that fibril can decompose and release antimicrobial peptides in the presence of bacteria for microbial membrane cleavage. Fibrils based on peptide assembly showed good and long-term antibacterial activity in terms of bacterial membrane destruction and bacterial calcium outflow.

Functional Small Molecule

In recent years, propelled by the interdisciplinary convergence of nanoscience, synthetic biology, and molecular engineering, significant advancements have been achieved in the development of intelligent self-assembly systems based on the synergistic integration of functional peptides and small molecules.[134] These systems, governed by precisely controlled intermolecular interactions including hydrogen bonding networks, π-π stacking, and hydrophobic forces, enable the meticulous manipulation of nanostructural morphology, resulting in the formation of hierarchically ordered architectures such as nanoparticles, microcapsules, and hydrogels with precisely controlled size distributions.[30] The exceptional biocompatibility and structural programmability of these systems demonstrate tremendous potential for applications in precision medicine, tissue engineering, and integrated molecular diagnostics and therapeutics.[135]

Drug Molecule

The peptide-drug self-assembly structure exhibits significant advantages, including enzymatic degradation stability, high drug loading capacity, controlled release properties, and superior biosafety, making it a prominent research focus in recent years.[136] For instance, Jiamin et al successfully conjugated the small molecule drug methotrexate (MTX) and the pH-responsive linker 2,3-dimethylmaleic anhydride (DA) to the KKFKFEFEF peptide chain through amidation reaction.[137] Upon reaching cancer cells, the molecule responds to the tumor's pH microenvironment, subsequently removing DA and undergoing in situ self-assembly to form hydrogels, thereby achieving sustained drug release for cancer cell eradication. Furthermore, XinXin et al engineered nanoparticles by assembling the conjugated dexamethasone (DEX) and FFFE sequences via ester bond linkage, demonstrating efficacy in treating endotoxin-induced uveitis in rabbits.[138] It is noteworthy that the selection of chemical bonds for conjugating drug molecules with peptide sequences significantly influences the properties of nanoassembled peptide materials. Matt et al conducted a comprehensive study on the conjugation of dexamethasone (DEX) with the self-assembly sequence VVVAAKK using ester and hydrazone bonds.[139] Their findings revealed that the selection of the linker significantly alters the precursor orientation, rotational degrees of freedom, and the number of stereoisomers in the final assembly. These modifications influence the assembly mechanism and energy barrier, as well as the nano/macroscale properties of the resulting molecular material. Beyond direct conjugation, drug molecules can also be coassembled with helper molecules through non-covalent interactions to form stable nanostructures. For instance, researchers have utilized π-π stacking interactions between the Q11 peptide (QQKFQFQFEQQ) and the local anesthetic ropivacaine monomer to create drug/peptide nanoparticles.[140] These nanoparticles can be mineralized by pH adjustment to form drug/peptide nanocrystals. Additionally, Meng et al encapsulated hydrophobic curcumin within the hydrophobic cavity of β-cyclodextrin (β-CD) as the core.[141] Hydrophilic EWDP was then absorbed into the region between the core and the chitosan derivative HTCC shell, forming amphoteric nanoparticles (NPs) through layer-by-layer self-assembly.

Fluorescent Molecule

In recent years, the advancement of novel optical nanoprobes has significantly propelled the evolution of nanoimaging technology. Among these, aggregation-induced emission luminogens (AIEgens) have gained extensive application in biological tracking, detection, and imaging owing to their exceptional photostability, sensitivity, and unique aggregation-induced luminescence properties.[142] Consequently, researchers have developed a series of AIEgen-peptide probes for TPE-G(x)f(y)pY(z)EEE, utilizing tetraphenylethene (TPE), a polymerization-induced emission material, based on structural alterations of self-assembled peptides.[142] These probes leverage the responsiveness of phosphate esters within the peptide sequence to alkaline phosphatase (ALP) for ALP content detection. Fluorescent based materials can be used for disease surveillance. Sun et al engineered a near-infrared fluorescent probe, 1FCG-FFGRGD, incorporating two functional peptide sequences.[143] The initial sequence, RGD, specifically targets and binds to the integrin αvβ3 receptor overexpressed on 4T1 breast cancer cells. Upon reaching a critical concentration, the secondary self-assembled sequence, FFG, facilitates the formation of β-sheet nanofibers through π-π stacking interactions. This probe orchestrates nanofiber construction within tumor lesions, enhances tumor site retention, and achieves superior signal-to-noise ratios for tumor imaging. In addition, the assembly process and mechanism of peptides have also been the core of research in recent years, and the use of fluorescent dyes can also be used to monitor the assembly process at the nanoscale. Mohit et al utilized the anionic sulfonate of Alexa-488 dye to electrostatically bind to the cationic sites of lysine (or arginine) residues exposed to the surface of peptide assembly nanostructures to achieve real-time monitoring of nanostructures in vivo.[144] The fluorescent properties of pyridine derivatives have also been used in the development of peptide assemblies. For example, Wei et al co-assembled functional bipyridine BPE and Fmoc-FF, and the assembly exhibited redox and photoresponsive properties, making it a promising candidate for future applications of controlled drug release and fluorescence patterning.[145] Tengyu et al co-assembled the LAGGGGFFPra peptide sequence with tetraphenylpyridine and proton sponge into a series of proton sponge nanoassemblies (PSNAs), which combined to make PSNAs have the highest fluorescence, positive surface charge density, cell absorption, and cancer cell killing functions (Figure 7a).[146]

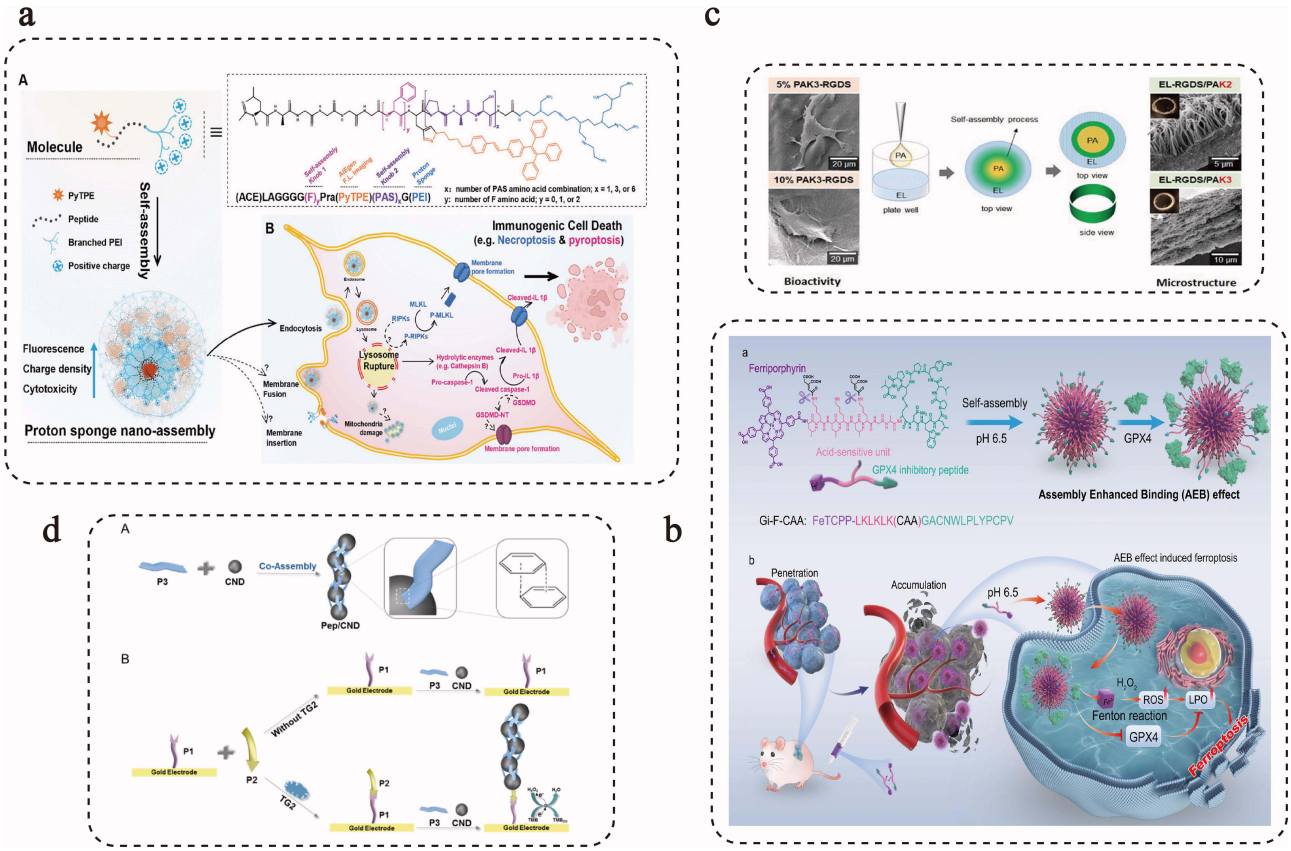

Figure 7 Co-assembly design strategy for multifunctional small molecules and assembled peptide sequences. (**a**) The LAGGGGFFPra peptide sequence and tetraphenylethylpyridine and proton sponges are co-assembled into a series of proton sponge nanoassemblies (PSNAs) that can be internalized by cancer cells through endocytosis to trigger necroptosis and pyroptosis, thereby releasing pro-inflammatory cytokines known to induce anti-cancer immunity. Reproduced with permission from Ref.[146] Copyright 2024, Wiley-VCH GmbH. (**b**) Gi-F-CAA is small in size and easy to penetrate into solid tumors. Gi-F-CAA self-assembles into large nano-particles in acidic tumor microenvironment to improve tumor endocytosis efficiency. Reproduced with permission from Ref.[147] Copyright 2024, Springer Nature. (**c**) The cell adhesion peptide RGDS was introduced into the molecular structure of peptide amphiphiles (PAs) and elastin like recombinants (ELs), and EL/PA co-assembled to form bioactive tubular membranes. Reproduced with permission from Ref.[148] Copyright 2023, The Authors. Published by American Chemical Society. (**d**) The non-covalent combination of peptides and carbon nanodots (CNDs) forms nanostructures. The obtained structures show the recognition ability of the peptide and the catalytic activity of CNDs, and have sensitive detection capabilities for transglutaminase 2. Reproduced with permission from Ref.[149] Copyright 2021, American Chemical Society.

Photosensitizer

Peptides can be used in the development of phototherapy drugs by conjugating photosensitizers. Porphyrins are a class of photosensitizers that can produce reactive oxygen species in response to light to treat cancer. Peptide-based assembly nanostructures can promote the trafficking, targeting, and uptake of photosensitizers, and increase their retention and accumulation in target tissues, thereby improving anti-tumor efficiency.[23] Jian et al co-assembled a simple amino porphyrin (m-TAPP) with a short peptide (Fmoc-L3-OMe) to form nanoparticles (NPs) with good biocompatibility and photoactivity.[18] Under light exposure, NPs induces ROS production, triggering damaging cancer cell ribosome damage and subsequent apoptosis to inhibit tumor growth. Da-Yong et al developed a peptide-ferroline conjugate, Gi-F-CAA.[147] In the acidic microenvironment of tumors, due to the enhanced hydrophobic interaction after hydrolysis of the pH-sensitive element CAA in the peptide side chain inhibited by glutathione peroxidase 4 (GPX4), Gi-F-CAA self-assembled into large nanoparticles to enhance its anticancer activity by improving tumor penetration, endothelial cell proliferation, and GPX4 inhibition, and finally by ferriproteinase (Figure 7b). Recently, researchers have developed a coupling-induced assembly (CIA) strategy to generate covalently cross-linked nanofibers, synthesized an antioxidant reactive peptide-porphyrin conjugate P1, and self-assembled into nanoparticles.[150] In the oxidizing microenvironment of mitochondria, the coupling of thiols in P1 leads to the formation of dimers, which are further ordered and stacked with translinked nanofibers. Under ultrasound (US) irradiation, porphyrin molecules in the shell produce a large amount of

reactive oxygen species (ROS), which act on adjacent mitochondrial membranes and exhibit 2-fold higher antitumor activity than nanoparticles in vitro and in vivo.

Other Molecule

The co-assembly of peptides with other biological macromolecules represents a promising approach for nanostructure formation. Monteiro et al demonstrated the synthesis of positively and negatively charged polysaccharide-peptide conjugates through Cu(I)-catalyzed azide-alkene cycloaddition, utilizing laminin (LAM) and pul marine polysaccharides with hexalysine (K6) or aspartic acid (D6) peptides, subsequently assembling them into multilayer films.[151] Majkowska et al achieved structural diversification in coassembled tubular membranes by implementing strategic modifications in peptide amphiphiles (PAs) and elastin-like recombinamers (ELRs).[148] Through precise adjustments of PA charge density (PAK2, PAK3, PAK4), distinct diffusion-reaction processes were initiated, yielding varied membrane microstructures. Furthermore, the combination of different PA types enabled structural and property optimization prior to ELR co-assembly (Figure 7c). Notably, researchers have successfully co-assembled lipopeptide PAs with soluble short peptide P1, generating supramolecular copolymers with tunable internal ordering.[152] At low peptide concentrations, these copolymers exhibit β-sheet stabilization within internal aqueous compartments, while higher concentrations induce copolymerization with lipid peptides, disrupting the β-sheet secondary structure. This thermodynamically driven co-assembly process facilitates spontaneous peptide monomer release, suggesting potential applications in drug delivery systems. Kulkarni et al employed click chemistry to synthesize lipidated β3-tripeptides from lactose and BDNF peptides via cleavable ester linkages, subsequently forming hydrogels capable of sustained, targeted peptide therapeutic release through endogenous esterase activity.[153] Additionally, peptide-nucleic acid co-assembly has been explored. As exemplified by Hanke et al's investigation of DNA origami structures (rod-shaped 6-helix bundles and triangular sheets) and their interaction with human islet amyloid polypeptide (hIAPP) in type 2 diabetes, examining their influence on hIAPP fiber aggregate formation.[154]

In addition to these conventional molecules, researchers have explored the co-assembly of materials with peptides to achieve enhanced functional diversity. Bhimareddy et al successfully conjugated diphenylalanine β and γ-peptides with carbon nanotubes (CNTs), resulting in the self-assembly of fibrous dendritic structures that facilitate the growth of primary hippocampal cells and modulate their neuronal functions.[155] Furthermore, the non-covalent integration of peptides with carbon nanodots (CND) has led to the formation of nanostructures that exhibit both peptide recognition capabilities and CND catalytic activity, demonstrating sensitive detection of transglutaminase 2 (Figure 7d).[149] Héctor et al engineered polyoxometalate (POM) and polypeptide K10 co-assemblies to form POMlymer nanoparticles, which not only enhance the intrinsic peroxidase-like activity of POM molecules but also exhibit potent antibacterial and anti-biofilm properties.[156] Additionally, researchers have utilized amino acid structural characteristics to modulate material physicochemical properties. For instance, Sayak et al coupled the well-characterized charge transport π system, Perylene diimide (PDI), with amino acids, enabling self-assembly in aqueous solutions.[157] Through the systematic conversion of coupled amino acids from glycine to alanine, they observed substantial variations in electronic properties, as evidenced by UV-visible spectroscopy, photoluminescence, and circular dichroism spectra. This pioneering work has significantly contributed to the advancement of short peptide research in this domain.

Assembly Design and Analysis Assistance

De Novo Design from Scratch

De novo peptide design is a technique for designing entirely new peptide sequences from scratch, based on the structure of peptides, using computational and theoretical methods, without relying on known peptide templates or structures.[158] A wide range of interactions are considered, such as van der Waals forces, hydrogen bonds, and electrostatic and aromatic interactions.[159] By predicting and optimizing the amino acid sequence, the peptide has a specific biological function or structural property. Supramolecular nanofibers based on self-assembling peptides designed from scratch are attractive biomaterials for tissue engineering, wound healing, and vaccines.[160] Takayuki et al reported a de novo peptide Y15 (YEYKYEYKYEYKYEY) that forms an amphiphilic beta chain with hydrophobic Tyr residues on one side and hydrophilic Glu and Lys residues on the other.[161] Thus, β-folded nanofibers are formed through hydrophobic and π-π

interactions, as well as electrostatic interactions of charged Glu and charged charges. The system provides a tool for organizing biologically functional supramolecular structures in living cells. Limin et al obtained bola-like peptides using de novo design and combinatorial chemical screening.[162] A series of assemblies with different tilt angles and β-sheet active sites were obtained by adjusting the surface area accessible to the solvent, including KYFYE and other peptides. Kuan et al obtained the self-assembled sequence Fmoc-R $(RCEX)_2$-NH_2 by de facto design and transformed from random coil to alpha helix structure by disulfide bonding of the lateral cysteine residue at the i/i+4 position.[163] The binding form of this peptide enforces conformational constraints, providing the driving force for self-assembly into nanorods/nanovesicles structures that can transport siRNA into cancer cells and release it. Based on de novo designed peptides, on the one hand, the theoretical knowledge has been summarized earlier, and the computer-aided design method is described in Section 2.4.2.

Bioinformatics Assistance

The design of self-assembled peptide molecules can be grounded in theoretical knowledge and enhanced through the application of bioinformatics and predictive software. In the process of self-assembly and peptide design, researchers can utilize the peptide structure-function prediction webpage and the protein structure prediction tool AlphaFold. For instance, Yuan et al employed AlphaFold2-assisted de novo design and precise morphological adjustment of acetate to develop an artificial peptide-assembled nanozyme, which integrates the antimicrobial effects of both antimicrobial peptides and enzymes within a single system.[164] The peptide, composed of three amino acids (His, Cys, and Ile) was predicted by AlphaFold2 to form β-sheets, a finding subsequently confirmed experimentally. With the advancement of bioinformatics, the use of computational methods, such as deep learning, to screen peptide sequences of interest has become a viable approach (Figure 8a). Rohit's team developed a machine learning workflow - AI Expert, which combines Monte Carlo tree search and random forests with molecular dynamics simulations.[165] This is a fully autonomous computational search engine to find peptide sequences with high self-assembly potential, from which several non-intuitive sequences with high self-assembly tendencies are obtained. Through bioinformatics tools and phylogenetic analysis, Shu et al identified GX8 peptides with GLYGGYGX sequences across various organisms.[166] These GX8 peptides can self-assemble into diverse supramolecular structures, exhibiting distinct physicochemical and viscoelastic properties, ranging from liquid-like co-aggregate microdroplets to hydrogels to rigid solid materials. Employing an AI-human negotiation approach, Lin et al designed a class of minimal model peptides targeting tuberculosis (TB), with K7W6 demonstrating potent efficacy, attributed to its assembly-inducing function.[167] In the prediction of assembly and the elucidation of self-assembly mechanisms, bioinformatics tools such as molecular dynamics (MD) analysis can be employed (Figure 8b). Divanach et al evaluated the autocorrelation behavior and differences between the aromatic-aliphatic Phe-Leu dipeptide and its reverse Leu-Phe and ring-ring (-Leu-Phe) counterparts using a combination of simulation and experimental methods.[168] Detailed all-atom molecular dynamics (MD) simulations quantitatively predict the conformational, kinetic, and structural properties of peptide self-assembly at the molecular level. Johannes' team also utilized the MD method in their study of the assembly process of silica particles containing RRIL peptides.[169]

The content of this section outlines the design strategies for self-assembling peptides, highlighting the diverse nanostructures that can be formed through peptide assembly, including nanofibers, nanosheets, nanospheres, vesicles, and hydrogels.[23,30] Each nanostructure possesses unique advantages; for instance, nanofibers and nanotubes facilitate gelation, making them highly promising for applications in biomedicine and voltage-responsive materials. Nanoribbons and nanosheets, with their high surface area and exposed active sites, are particularly suited for supporting active molecules. Vesicle structures, characterized by their hydrophobic pockets, are widely utilized in drug delivery systems.[30] While this paper does not delve into the specifics of assembly forms, readers are encouraged to consult an excellent review for further details.[3]

Comprehensive Design Strategy

From the design perspective and strategic approach of self-assembling peptides previously discussed, peptide assembly systems engineered through dual or multiple strategies offer enhanced structural and functional versatility. For instance, Gao et al developed a novel molecular construct, biotin-LYS (SA-Cip-OH) -Lys (SA-CPT) -Phe-Nap (Biotin-Cip-CPT-

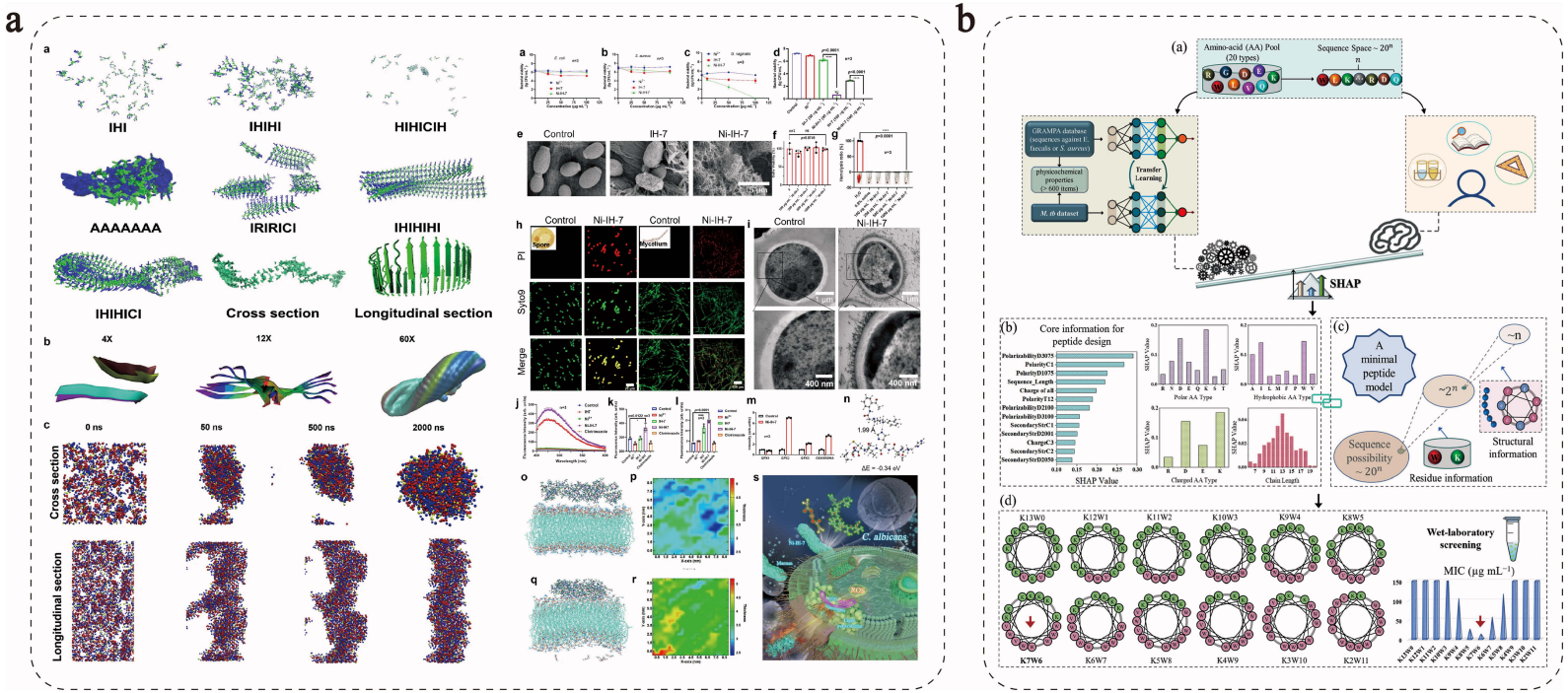

Figure 8 Bioinformatics assistance. (**a**) The possible three-dimensional structure of various peptide sequences predicted by AlphaFold2, simulation of IHIHICI (IH-7) aggregation, MD simulation of converting dynamic assembly into IH-7 macroscopic structures, and systematic evaluation of the antibacterial properties of Ni-IH-7 nanotubes and their mechanism of action. Reproduced with permission from Ref.[164] Copyright 2024, The Authors. (**b**) By applying the "AI-Human negotiation" framework and combining with SHAP analysis, an efficient anti-tuberculosis antimicrobial peptide represented by K7W6 was rationally designed. K7W6 possesses outstanding in vivo and in vitro activity, low cytotoxicity, and can produce a synergistic effect with the first-line antibiotic ripicin. Reproduced with permission from Ref.[167] Copyright 2024, American Chemical Society.

Nap), aimed at overcoming chemotherapeutic drug resistance induced by bacteria and enhancing anti-tumor immunity.[170] This design incorporates four functional motifs: a targeted biotin motif, a Phe (-Nap) motif for self-assembly, a ciprofloxacin derivative motif for antibacterial action, and a camptothecin motif for chemotherapy. By utilizing this engineered molecular combination, an innovative strategy was achieved for the formation of intracellular enzymatic nanofibers and the synergistic enhancement of antimicrobial effects in both chemotherapy and immunotherapy. Similarly, Wang et al developed an HD-6 mimetic peptide (HDMP) that effectively recognizes and entraps bacteria in vivo.[171] HDMP (dipyrene-KLVFF-RLYLRIGRR) comprises three key components: a dipyrene motif, a self-assembling KLVFF unit, and a recognition unit RLYLRIGRR that specifically binds to lipoteichoic acid (LTA) as a ligand for Gram-positive bacteria. Initially, HDMPs self-assemble into nanoparticles (HDMP NPs) in aqueous solution. These HDMP NPs subsequently transform into in-situ nanofibers with β-sheet secondary structures upon LTA-specific binding to Gram-positive bacteria, such as Staphylococcus aureus, via ligand-receptor interactions.

Limin et al developed a multifunctional self-assembled peptide nanomedicine for cancer therapy based on immune cell death (ICD) by incorporating multiple strategies targeting peptides, chirality, phosphatase response, and drug small molecule co-assembly.[172] The specific targeting sequences NTYYEDQG and TPP in this system achieve double targeting of cell membrane and mitochondria, and the core motif of $G^{D}F^{D}Fp^{D}Y$ assembly is alkaline phosphatase responsive, while carrying Lonidamine (LND) that specifically interferes with mitochondrial function. This multifunctional model not only allows for in-situ construction of peptide assemblies within mitochondria, but also precisely delivers LND into mitochondria, resulting in mitochondrial dysfunction, ICD response, immunogenic TME, and systemic anti-tumor response. This system develops mitochondria-specific ICD inducers through a cascade targeting approach and provides an effective strategy to optimize the therapeutic efficacy of current mitochondrial and other organel-specific ICD inducers.

Wenjun's team proposed a tandem guest-host-receptor recognition strategy by combining multifunctional molecules such as drug molecules, host-guest recognition units, and enzyme response sequences to precisely guide ciprofloxacin to effectively eliminate intracellular *Staphylococcus aureus*.[173] The designed Cip-CBT-Ada consists of five motifs: ciprofloxacin, CBT motif, guest motif adamantane (Ada), StBu-protected cysteine residues, and Tyr-val-ala-Asp sequence with caspase-1 enzyme response activity. Through guest-host recognition, Cip-CBT-Ada is modified with a β-cyclodextrin-hepmannanoside (CD-M) derivative to produce Cip-CBT-Ada/CD-M, which is able to target macrophages overexpressing mannose receptors via multivalent ligand-receptor recognition. Subsequently, the CBT-Cys click reaction initiated by the digestion response is self-assembled into ciprofloxacin nanoparticle nanoCip. In vivo and in vitro, it showed excellent intracellular bacterial elimination and inflammation alleviation efficiency.

Zhang et al developed a peptide-antibody combination-supramolecular in situ assembly dual-target inhibitor targeting CD47 and CD24 (PAC-SABI), utilizing an integrated system comprising targeted peptides, PEG co-group modifications, fluorophores, monoclonal antibody molecules, and enzyme-responsive elements.[174] The peptide backbone was constructed with a lys-leu-val-Ph-phe sequence, facilitating molecular assembly. Both termini were functionalized with NBD and Cy5.5 fluorophores, respectively, enabling real-time fluorescence imaging. PEG2000 was incorporated to enhance the drug's circulation time in the bloodstream and augment tumor accumulation. The specific binding peptide Pep-20 was designed to target CD47 and inhibit the CD47/SIRPα interaction. Furthermore, active targeting of CD24-overexpressing cancer cells was accomplished through conjugation with anti-CD24 monoclonal antibodies. The tyrosine residue in Pep-20 is susceptible to phosphorylation, which promotes in situ molecular rearrangement and assembly growth via alkaline phosphatase-mediated dephosphorylation. This system facilitates biomimetic surface propagation on cancer cell membranes through ligand-receptor binding and enzyme-triggered reactions, while mediating conformational maturation through target binding and enzymatic catalysis, thereby achieving in situ self-assembly and presentation of bioactive moieties.

Application Development of Peptide-Based Assembly Materials

Self-assembled peptides have demonstrated extensive application potential across multiple disciplines, particularly in biomedical and materials science domains.[175] Within the realm of nanomedicine, these peptides have emerged as optimal building blocks for constructing intelligent nanomaterials due to their structural simplicity, sequence tunability, superior biocompatibility, and facile chemical modification capabilities.[25] Through bottom-up assembly strategies, they can form supramolecular architectures for diverse applications including drug delivery systems, gene therapy platforms, targeted cancer treatments, and vaccine

development, achieving therapeutic synergies.[30] Their utility extends to tissue engineering, biosensor development, and environmental science applications, owing to their controllable self-assembly processes, biomimetic properties, and exceptional degradation characteristics.[175] In materials science, hybrid peptide systems have been implemented in emerging technologies including semiconductor devices, piezoelectric systems, and optoelectronic applications, demonstrating remarkable thermal and mechanical stability through precise regulation of secondary structures and nanoscale morphologies.[52,176] This multifunctionality originates from their precise supramolecular structural design and the flexible integration of biochemical functionalities, establishing them as a crucial platform for interdisciplinary research endeavors (Figure 9).

Disease Treatment

Diagnosis and Treatment of Cancer

As a predominant cause of global mortality, cancer presents significant challenges in therapeutic intervention and monitoring. Conventional chemotherapeutic agents are frequently associated with systemic toxicity, adverse effects, and limited therapeutic efficacy, primarily attributable to poor solubility, short half-life, inadequate tumor penetration, and lack of target specificity. In this context, self-assembled peptide nanomaterials have emerged as innovative solutions for cancer diagnosis and treatment, owing to their distinctive advantages.[177] Compared to traditional inorganic or polymeric nanomaterials, peptide-based nanoparticles exhibit superior biocompatibility, biodegradability, and low immunogenicity, effectively addressing long-term safety concerns.[175] Their advantages are further manifested in sequence programmability, dynamic environmental responsiveness, high drug-loading capacity, synergistic effects, and multifunctional integration.[177] Examples include the work by Song et al, who utilized enantiomeric amphiphilic peptides

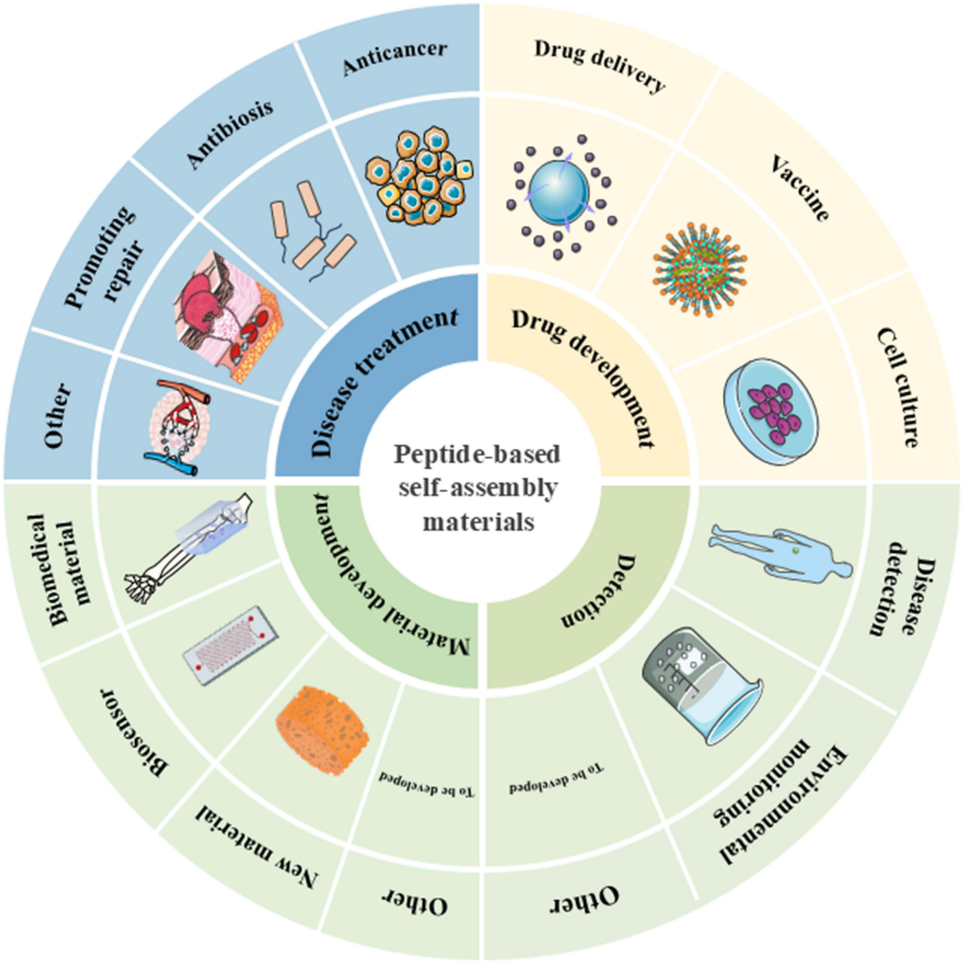

Figure 9 Multi-field application and development of peptide-based assembly materials.

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R3R6 and r3R6 as the peptide core system, connected via C-terminal disulfide bonds.[178] These peptides electrostatically bind to negatively charged plasmid DNA (TF pDNA) to encapsulate the hydrophobic core of the two aggregates containing the chemotherapeutic agent paclitaxel (PTX). Upon internalization by tumor cells, the disulfide bonds in R3R6 and r3R6 are cleaved by intracellular GSH, leading to the separation of arginine sequences. This transformation from nanoparticles to nanofibers facilitates the co-release of TF pDNA and PTX, thereby inhibiting cancer cell proliferation. Additionally, Man-Di et al engineered a bispecific assembly peptide, anti-CD3-G7-RGD, by conjugating the CD3 antibody to the peptide GNNQQNY and the αVβ3 integrin-targeting RGD peptide.[179] This assembly induces CD3 oligomerization and subsequent T cell activation, culminating in T cell-mediated cancer cell lysis.

In the field of cancer monitoring, self-assembled peptides have demonstrated significant potential in constructing highly sensitive biosensors through biomimetic design and functionalization strategies. Electrochemical sensing technology has emerged as a pivotal approach for real-time monitoring of both intracellular and extracellular bioactive molecules. Tian et al developed a multi-stage recognition and morphologically transformable self-assembled peptide nanobiosensor (NDRP), which incorporates a novel peptide sequence DRP and the hydrophobic responsive fluorophore 4-chloro-7-nitro-2,1,3-benzooxadiazole (NBD).[180] This innovative biosensor exhibits specific responsiveness to epithelial-mesenchymal transition (EMT) markers and demonstrates targeted cytotoxicity towards mesenchymal tumor cells in vivo. The peptide architecture features a molecular switch that can be specifically activated by receptor binding, facilitating vesicle-to-fibril transformation within living systems under enhanced fluorescence signaling (Figure 10a).

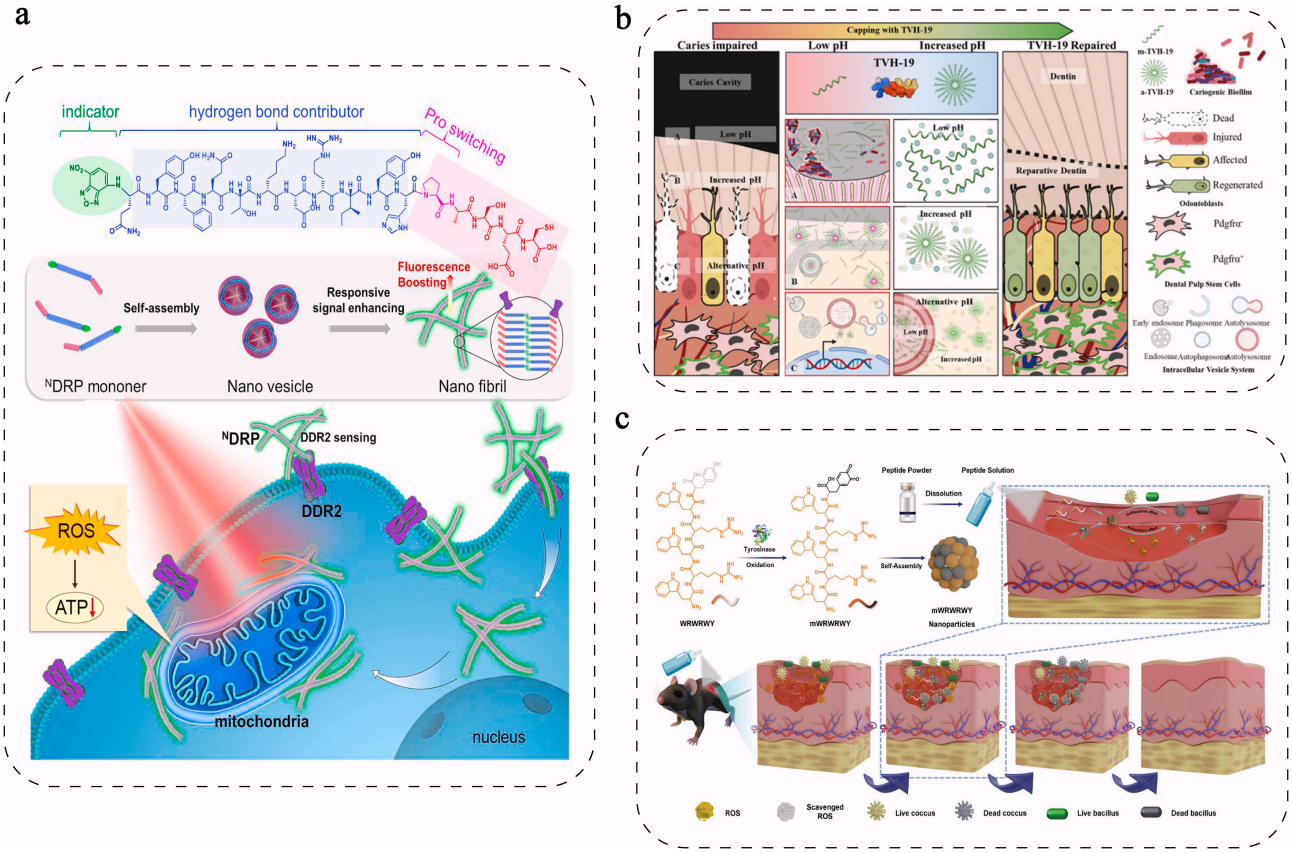

Figure 10 Application of peptide-based self-assembly materials in the treatment of diseases. (**a**) Schematic diagram of a nanosensor. NDRPS can first be recognized and triggered by DDR2, then converted from nanovesicles to nanofibril and emit an enhanced fluorescence signal. NDRP can also achieve and damage mitochondria. Reproduced with permission of Ref.[180] Copyright 2021, Elsevier. (**b**) The peptide TVH-19 exhibits a multifunctional mechanism based on pH-responsive self-assembly: in acidic environments, it remains in a monomeric form that exerts antibacterial effects and penetrates cells; under neutral conditions, it self-assembles into nanoparticles that induce the differentiation of dental pulp stem cells. Reproduced with permission from Ref.[181] Copyright 2024, American Chemical Society. (**c**) At the wound site, the WRWRWY peptide aqueous solution self-assemples into mWRWRWY nanoparticles due to the oxidation of tyrosinase. Peptide nanoparticles can remove superoxide free radicals, hydroxyl free radicals and H_2O_2, and can effectively heal infected wounds and significantly reduce ROS. Reproduced with permission from Ref.[182] Copyright 2023, Wiley-VCH GmbH.

Anti-Microbial

It is an effective means to obtain stable and effective antimicrobial materials by using the self-assembled nanomaterials of antimicrobial peptides and their modified peptides. Xiaoyan et al conjugated the antimicrobial peptide LKLLKKLLKKLKK with polyethylene glycol and chitosan to form nano-assembly structures in an aqueous environment.[183] When the nanoassembly encounters the fungal hyphae, it decomposes on the fungal cell membrane, revealing the α-helical peptide, which destroys the cell membrane and kills the fungus. It has also shown good therapeutic efficacy in ocular animal models of fungal infection. Lucia et al added six hydrophobic alanine and alkyl chain C19 to the C-terminus of the natural antimicrobial peptide MWR, which can self-assemble into stable nanofiber structures.[184] This nanofiber pair is able to eradicate the biofilm that has been formed by the green false negative bacteria and Candida albicans, and has good antimicrobial activity. The Sili team derived the cell-penetrating self-assembling peptide TVH-19 from the amelogenin peptide.[181] Leveraging TVH-19's unique amphotelist-associated cell permeability and ionic/pH responsive self-assembly properties, the TVH-19 nanostructure enables rapid cell permeation, minimizes diffusion side effects, provides environmentally responsive self-assembly/disassembly to balance long-term antimicrobial and cellular protection, and promotes the formation of lysosomal escape cell endoglomers for sustained activation of PDGFRα+ dental pulp stem cells (Figure 10b).

Promote Growth/Repair

Peptide self-assembly materials demonstrate distinctive advantages in facilitating tissue growth and repair. Owing to their injectable characteristics, biocompatibility, and inherent tissue mechanics, peptide-based biomaterials serve as effective delivery vehicles for growth factors and nutrients, while enhancing cellular signaling through the simulation of growth factor structures or binding to surface receptors.[22] Jacob et al employed a bioactive peptide ampholytic supramolecular polymer that exhibits specific binding affinity for chondrocytokine transforming growth factor β-1 (TGF-β-1).[185] When further combined with hyaluronic acid to form injectable hydrogels, these composites facilitate the formation of filament bundles, a hierarchical architecture prevalent in natural musculoskeletal tissue that significantly promotes cartilage regeneration. Ariel et al designed six self-assembling peptides, including FAQRVPPGGG$(LDLK)_3$-$CONH_2$, and demonstrated that these peptides effectively promote the migration of endothelial cells, macrophages, fibroblasts, and neuron-like cells in vitro, exhibiting substantial potential for supporting tissue regeneration.[186]

Furthermore, the strategic design of peptide-based materials in vascular regeneration facilitates the localized accumulation of VEGF and other growth factors, thereby enhancing vascular endothelialization and functional restoration.[187] For instance, Bin et al engineered a hydrogel by integrating the angiogenic peptide GEETEVTVEGLEPG with a β-sheet structural peptide, which undergoes self-assembly under pH stimulation.[188] This hydrogel has demonstrated significant angiogenic potential in both in vivo and in vitro studies. Concurrently, short self-assembling peptides are gaining increasing recognition as novel hemostatic agents. Such as, the high-density nanofibers formed by the classic EAK16 peptide in blood exhibit a multi-layered network structure analogous to fishing nets, effectively promoting blood coagulation and preventing the escape of blood cells and biomolecules from wound sites.[189] Yu Chuan's research team achieved significant advancements by co-assembling poly-L-lysine with sulindac to form poly-L-Lysine/SUL nanoparticles, which demonstrated enhanced targeting capability to bleeding sites and improved hemostatic efficiency across various in vivo bleeding models.[190] Peptides exhibit diverse biological activities, including immunoregulation and anti-inflammatory properties, making them promising candidates for developing self-assembling peptide materials for wound healing applications. For example, Yu et al extracted cyclic antimicrobial peptides (CAPs) featuring supramolecular random self-assembly sequences from *Crassostrea gigas*.[191] These CAPs exhibit antioxidant and anti-inflammatory properties, promote fibroblast proliferation, and facilitate vascular remodeling. Furthermore, they demonstrate significant efficacy in enhancing skin wound healing. Additionally, Teng et al developed an innovative antimicrobial peptide nanoparticle using the short antimicrobial peptide WRWRWY, which undergoes in situ oxidation and self-assembly into mWRWRWY nanoparticles upon activation by skin surface tyrosinase.[182] These nanoparticles exhibit enhanced antibacterial activity, superior antioxidant capacity, and low toxicity, effectively promoting the healing of infected wounds (Figure 10c).

Other Diseases

The limitations of current vitreous substitutes substantially compromise the post-vitrectomy outcomes in vitreoretinal diseases. Yuting et al developed an innovative self-assembling peptide hydrogel (3E-OX) characterized by a three-dimensional network architecture and exceptional water retention capacity.[192] This engineered peptide hydrogel exhibits remarkable similarity to natural vitreous properties, demonstrating superior optical transparency, porous morphology, and enhanced permeability, thereby facilitating metabolic exchange and ensuring biocompatibility, making it a promising vitreous substitute. Regarding urological procedures, circumcision, while common, may lead to severe postoperative complications such as persistent foreskin edema, significantly affecting patients' quality of life. Jianyong et al synthesized an amphiphilic hexapeptide (Ac-FFFGHK-OH) through N-terminal modification of hydrophilic bioactive GHK and hydrophobic assembly of Ac-FFF-OH.[193] The spontaneous self-assembly of Ac-FFFGHK-OH in saline solution yielded helical nanofibers and chiral nanofiber hydrogels. This hydrogel effectively alleviates post-circumcision edema in rat models, attributed to its biocompatibility, promotion of endothelial cell migration and tube formation, and anti-inflammatory properties. The development of biomimetic therapeutic gas-releasing peptide-based nanomaterials tailored for specific tissues and organs is crucial for targeted disease treatment. The Inhye team engineered visible light-crosslinked supramolecular CORH, utilizing self-assembled nanofibrils with Y-containing peptides derived from natural elastin.[194] This approach resulted in stable nanofibers, enhancing the hydrogel's mechanical strength and stability while precisely regulating its CO release kinetics. The therapeutic CO gas release from CORM or CORM-based nanoscaffolds can be precisely modulated through controlled water exchange processes. In parallel, Hao et al designed and synthesized a hexapeptide, PM^{SeO}, incorporating a mitochondria-targeting N-methylpyridine moiety and two GSH-reactive seleno-oxygen groups.[195] Upon cellular internalization, the hexapeptide undergoes GSH-mediated reduction, triggering redox-responsive self-assembly into nanoribbons through the conversion of hydrophilic selenium oxides to hydrophobic selenide groups. This process facilitates reversible oxidation by residual mitochondrial ROS, enabling peptide dissociation from mitochondria and subsequent cytoplasmic re-entry for GSH reduction. This dissipative self-assembly mechanism effectively reduces elevated ROS levels and downregulates proinflammatory cytokine expression.

Drug Development

Drug Delivery

Self-assembling peptides exhibit distinctive advantages in the field of drug delivery, with their diverse nanostructures capable of modulating drug distribution and localization through size, charge, and surface chemistry.[26] The hydrophobic domain of peptide assemblies can encapsulate hydrophobic drugs (eg, the chemotherapeutic agent paclitaxel) and enhance drug loading capacity through covalent coupling strategies.[196] For instance, Wang et al developed biodegradable nanoparticles utilizing amphiphilic copolymers composed of glutamic acid, lysine, histidine, and polyethylene glycol.[197] The hydrophobic core of these nanoparticles effectively encapsulates DOX, enabling pH-responsive drug delivery to the tumor microenvironment. These nanoparticles demonstrate stability at physiological pH with minimal drug leakage, while efficiently releasing their payload under acidic conditions, thereby significantly inhibiting the growth and metastasis of breast cancer cells. Li et al engineered positively charged nanoparticles through the co-assembly of glycopeptides (Mannose-AANLVFF), cationic peptides (RTT-AANLVFF), and DOX, which exhibit high cellular penetration and specific targeting of M2 macrophages in the fundus.[198] Through M2 macrophage-specific mannose receptor-mediated phagocytosis and asparagine endopeptidase recognition, these nanoparticles undergo transformation into nanofibers, thereby achieving prolonged retention in the lesion area (Figure 11a). Regarding the delivery of protein and nucleic acid therapeutics, peptide assembly systems can preserve protein activity under mild assembly conditions, ensure biosafety, and facilitate targeted release.[199] For example, Ankan et al designed guanine-terminated polyaspartic acid micelles for direct cytoplasmic delivery of proteins and DNA, where polymers form nanoassemblies to deliver proteins/DNA directly to the cytoplasm (Figure 11b).[200] A pure peptide, designated as (HR) 3gT, has the ability to self-assemble into nanoparticles known as MCM-NP.[201] These nanoparticles are capable of capturing both single-stranded and double-stranded DNA up to a length of 100 nucleotides. The process of DNA capture is primarily governed by electrostatic interactions between the DNA and the peptides, as well as the solvent conditions employed during self-assembly. These amphiphilic peptide nanoparticles represent promising candidates for future systemic gene delivery

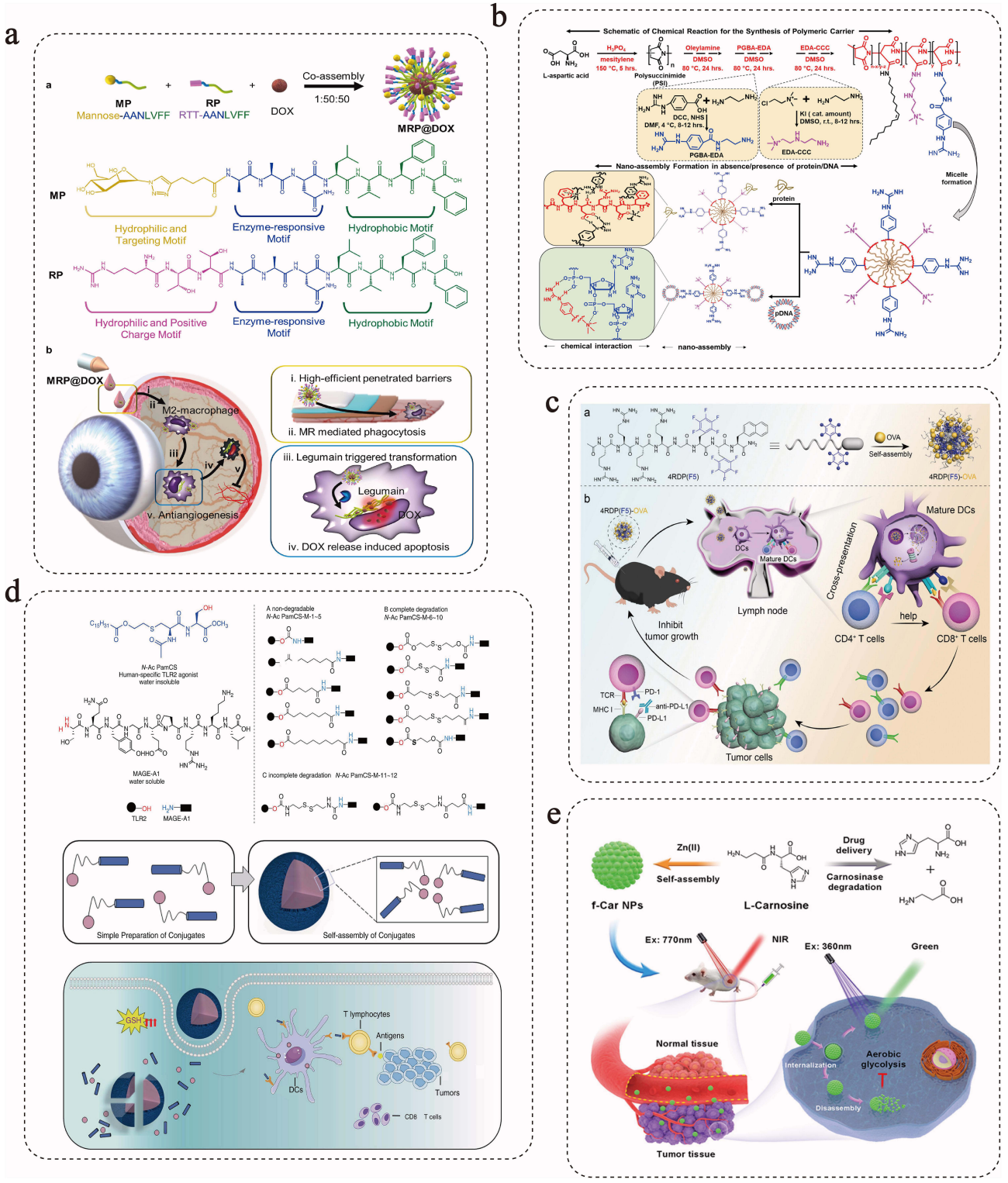

Figure 11 Application of peptide-based self-assembly materials in drug development. (**a**) Glycopeptide (Mannose-AANLVFF), cationic peptide (RTT-AANLVFF) and doxorubicin (DOX) are co-assembled as positively charged nanoparticles with high cell penetration and can specifically target M2 macrophages in the fundus. Reproduced with permission from Ref.[198] Copyright 2021, Elsevier. (**b**) Guanidin-terminated polyaspartic acid micelles are used for direct cytoplasmic delivery of proteins and DNA. Reproduced with permission from Ref.[200] Copyright 2022, American Chemical Society. (**c**) 4RDP (F5) -OVA nanovaccine is used in the treatment of tumor, with high intracellular uptake rate, good efficiency of antigen cross-presentation and large activation of CD8 T cells. Reproduced with permission from Ref.[203] Copyright 2023, Wiley-VCH GmbH. (**d**) The structure of target coupler and antigenic peptide and TLR2 agonist are self-assembled into nanoparticles for cancer immunotherapy. Reproduced with permission from Ref.[204] Copyright 2023, John Wiley & Sons Ltd. (**e**) Carnosine self-assembles with Zn (II) to construct f-Car NPs by zinc coordination and π-π stacking. f-Car NPs can accumulate in tumor tissue due to EPR effects, which can be monitored by NIR fluorescence of f-Car NPs. f-Car NPs can then be internalized, broken down, and released by tumor cells to inhibit aerobic glycolysis.[205] Copyright 2021, American Chemical Society.

https://doi.org/10.2147/IJN.S569237

applications. Furthermore, Yang et al successfully developed a nanoantibody-controlled and sustained-release hydrogel system based on ultra-acidic $(RADA)_5$ self-assembling peptides, demonstrating significant potential as a controllable nanobody delivery system in the gastrointestinal tract.[202] The $(RADA)_5$ peptide self-assembles into β-sheet structures, forming fibrous, intertwined hydrogel networks at extremely acidic pH. This hydrogel system releases approximately 80% of nanoantibodies at pH 6.8 while retaining less than 30% at pH 2.0, enabling nanoantibody retention in the acidic stomach and targeted release in the intestinal environment.

Vaccine

Peptide self-assembly technology has demonstrated distinctive advantages in vaccine development. The fibrous peptide nanostructures formed through self-assembly can be efficiently phagocytosed by immune cells, including neutrophils and lymphocytes, thereby facilitating antigen delivery, activating immune responses, and serving as effective adjuvants to enhance vaccine efficacy.[206] Shaorui et al developed a series of peptide adjuvants derived from arginine (R) and fluorinated diphenylalanine peptides (DP).[203] Among these, 4RDP (F5) exhibited the strongest binding affinity with the model antigen ovalbumin (OVA) and demonstrated optimal efficacy in dendritic cell maturation and antigen-lysosome escape. Consequently, the 4RDP (F5)-OVA nanovaccine elicited robust cellular immunity in a prophylactic OVA-expressed EG7-OVA lymphoma model, resulting in long-term immune memory against tumor behavior (Figure 11c). In a separate study, the MAGE-A1 peptide was covalently coupled with a TLR2 agonist, yielding 12 conjugates with self-assembly properties.[204] All developed conjugates formed spherical nanoparticles that significantly enhanced the efficacy of peptide vaccines. Notably, N-Ac PamCS-M-6 markedly promoted dendritic cell maturation, $CD8^+$ T cell activation, and tumor cell killing (Figure 11d). The Ximena team further engineered nanorods through the self-assembly of a 10-mer β-sheet sequence and a highly conserved epitope from influenza A virus (M2e), with M2e positioned externally.[207] This assembly was efficiently absorbed by antigen-presenting cells, and the cross-β quaternary structure activated toll-like receptor 2, stimulating dendritic cells. Subcutaneous immunization in mice elicited a robust M2e-specific IgG response.

Cell Culture

In the domain of cell culture scaffolds, self-assembled peptides have emerged as an optimal three-dimensional growth platform, owing to their intrinsic biocompatibility and modifiable chemical properties, which facilitate the targeted proliferation of diverse cell lines and precisely enhance the specific recognition and adhesion of cell surface molecules.[208] Numerous systems based on self-assembled peptides have been developed for cell culture applications. For instance, the Yamada research group engineered a negatively charged, self-assembled peptide, AcVES3-RGDV, through de novo design. During the peptide-induced self-assembly process, cells are readily encapsulated.[209] Self-assembly is triggered by modulating the ionic strength and/or temperature of the solution, while maintaining minimal pH fluctuations. AcVES3-RGDV gels enable cellular material attachment and serve as an exceptional system for both 2D and 3D cell cultures. Cosimo et al employed the metal chelator tetrasodium ethylenediaminetetraacetic acid (Na_4EDTA) to induce hydrogel formation with the peptide $C_{15}H_{31}CONH$-VVVAAAEEE-$CONH_2$.[210] This hydrogel functions as a 3D matrix for mammalian cell growth, permitting detachment for cell extraction, expansion, characterization, and manipulation.

Detection

Peptide self-assembly technology has shown a wide range of application potential in the field of detection, covering multiple dimensions from disease diagnosis to in vitro environmental monitoring. Among them, cancer marker detection is an important application direction of this technology, and many innovative research results have been made. Liang et al designed an amphoteric peptide C_{16}-Pep-Fc in which the alkyl chain C_{16} forms a hydrophobic core to form nanospheres, and the hydrophilic fragments Pep and Fc tags are exposed on the outer surface.[211] The nanospheres can be ultra-sensitive to recognize the melanoma marker protein S100B for the detection of melanoma in vitro and in vivo. Fluorescent labeling has become a key strategy to achieve higher sensitivity detection targets. For example, Rita's team linked the cyanamide dye Cy5 to the C-terminus of a pH-sensitive peptide designed by de novo.[212] The peptide is

assembled into branchless compact layered rods at pH 7.4 and forms a two-dimensional membrane at pH 3.4. Both nanomorphologies exhibit spectral signatures of H aggregates. These synthetic polychromophores can be further applied in artificial light acquisition devices, organic optoelectronics, tumor imaging, and other fields.

It is worth noting that some non-fluorescent peptides can produce optically active nanostructures through the self-assembly process, and this characteristic transformation mechanism provides a new idea for the construction of a multifunctional integrated diagnosis and treatment platform. For example, Weifeng et al self-assembled the antitumor dipeptide carnosine into nanoparticles in a zinc ion environment (Figure 11e).[205] The nanoparticles exhibit fluorescence in the visible and near-infrared (NIR) ranges for in vitro and in vivo fluorescence tracking. Similarly, aromatic cyclic dipeptides have luminescent properties, such as cyclic tryptophan (cyclo-WW), cyclodiphenylalanine (cyclo-FF), and cyclic dihistidine (cyclic HH).[213,214] These cyclic dipeptides are dimerized into quantum dots, and by modulating the self-assembly process, the emission can be adjusted from the visible region to the near-infrared region (420 nm to 820 nm). In addition, these nanostructures are used for in vivo imaging and as phosphors for light-emitting diodes. In addition, the band gap can be adjusted by Zn(II) to alter the light absorption and luminescence properties of cyclic dipeptide-based QC components. The fluorescence method developed based on this is a biocompatible alternative for the rapid detection of trace contaminants. The detection of hydrogen peroxide (H_2O_2) is of great significance in environmental monitoring, enzymatic reactions, and disease diagnosis. Danzhu et al self-assembled nanofibers (PNFs) by KIIIIKYWYAF sequences as bridges for ultrafine platinum nanowires (PtNWs) in graphene oxide (GO).[215] Together, they form PtNWs-PNFs/GO hybrids. The synthesized PtNWs-PNFs/GO hybrids can catalyze the decomposition of H2O2 to generate OH radicals with significant current response. OH radicals are able to be over-oxidized to produce a blue species, 3,3',5,5', -tetramethylbenzodine (TMB), with a pronounced color change, for colorimetric detection.

Material Development

Self-assembled peptides have demonstrated extensive application potential across various high-tech domains owing to their superior biocompatibility, tunable optical properties, and inherent safety.[28] In the biomedical field, materials derived from these peptides have been effectively utilized in the development of bone tissue engineering scaffolds, bioadhesives for wound closure, and medical-grade protective films.[216–218] In the realm of analytical detection, specific fluorescent probes and biosensors can be engineered through precise molecular design.[219,220] Within advanced manufacturing, this material system offers a novel bio-ink solution for 3D bioprinting, while its distinctive electrospinning characteristics further broaden the fabrication pathways for nanofiber materials.[221] Notably, in the field of new energy, peptide-based composites exhibit exceptional electron transfer efficiency in electrocatalytic reactions due to their well-ordered nanostructures, presenting innovative concepts for the development of green energy devices.[222] Representative applications of self-assembling peptides in these domains are systematically summarized in Table 1.

Table 1 Application of Self-Assembling Polypeptides in the Field of Materials

Application	Peptide	Functional Molecule	Type of Assembly	Structure	Responsive	Ref.
Bonelike material	$(Pro\text{-}Hyp\text{-}Gly)_{10}$	-	Self-assembly	Hydrogel	Spontaneous	[216]
	NapFFY	SDF-1 and BMP-2	Co-assembly	Hydrogel	pH/ Temperature	[223]
Adhesive materials	P1-P7	Zein/SDS	Co-assembly	Colloid	pH	[217]
	Pep1 and Pep2	Polyoxometalate $K_6H[SiW_9V_3O_{40}]$	Co-assembly	Adhesive	pH/ Temperature	[224]
	A_C-RRYNYQRR-NH_2	Glycyrrhizic acid (GA)	Co-assembly	Adhesive	Spontaneous	[225]
	FFpS, FYpS or YYpS	Positively charged proteins (PCP)	Co-assembly	Adhesive	Spontaneous	[218]

(*Continued*)

Table 1 (Continued).

Application	Peptide	Functional Molecule	Type of Assembly	Structure	Responsive	Ref.
3D printing	$K_2(SL)_6K_2$ and $E_2(SL)_6E_2$	-	Co-assembly	Hydrogel	Salt ion/pH	[221]
	CH-01 and CH-02	-	Self-assembly	Hydrogel	Solvent	[226]
Film	DFNKF, DF(I)NKF, DF(F5) NKF	Cellulose nanofibers (CNF)	Co-assembly	Hydrogel	Spontaneous	[227]
Biosensor	cyclo-YY	-	Self-assembly	Nanofiber	Temperature/ Light	[219]
	GSH	TPE	Self-assembly	Nanoparticle	Solvent	[228]
Piezoresistive Sensor	Fmoc-FF	2D Ti3C2Tz MXene nanosheets	Co-assembly	Hydrogel	Solvent	[229]
Fluorescent probe	GYK	-	Self-assembly	Nanoparticle	OH	[220]
Electrospinning	Nap-FFGRGD	Poly (ε-caprolactone) (PCL)	Self-assembly	Nanofiber	Temperature	[222]
Electrocatalysts	LMLHLFL, LILHLFL, LHLHLFL and VHVHVYV	Graphite electrodes and hemin	Self-assembly	Nanosheet	Spontaneous	[230]
Peptide-π-conjugated materials	DAVG/GVAD or DAIA/AIAD	Perylene diimides (PDIs)	Self-assembly	J aggregates or liquid-crystalline-type	Light	[157]

Challenges and Prospects of Peptide-Based Self-Assembly Materials

Peptide self-assembly, as a cutting-edge frontier in the design and functional regulation of biomimetic materials, provides a fundamental insight: a programmable coupling exists among molecular sequences, non-covalent interactions, and macroscopic structures. By employing molecular design strategies—including amino acid sequence optimization, side chain modification, amphiphilicity tuning, and chirality induction—precise control over assembly kinetics and material functionality can be achieved. This review highlights that the unifying principle underlying polypeptide self-assembly is the translation of molecular-level structural information into predictable, hierarchically ordered architectures, enabled by non-covalent interactions such as hydrogen bonding, hydrophobic effects, and π–π stacking. Furthermore, these interactions facilitate the dynamic integration of functional modules. The intrinsic interplay among molecules, structures, and functions establishes a robust theoretical framework for developing intelligent and programmable biomimetic materials.

Looking ahead, the advancement of polypeptide self-assembled materials will increasingly depend on rational and predictive design methodologies. Future research should integrate experimental and computational approaches, leveraging hybrid models that combine machine learning with molecular dynamics simulations to enable rapid screening of amino acid sequences, accurate prediction of assembly structures and energy stability at the design stage, and thus significantly reduce the time and cost associated with iterative experimentation. In structural engineering, the development of modular and stimuli-responsive design strategies is recommended to allow precise control over assembly processes and functional transitions in response to external cues such as pH, temperature, or enzymatic environments, thereby enhancing the adaptability and application versatility of these materials.

At the same time, more in-depth investigation into the assembly behavior of polypeptides within real physiological environments is required. For example, it is essential to examine how factors such as enzymatic degradation, variations in ionic strength, and fluid flow influence the structural stability and biological activity of assemblies, thereby guiding the rational design of more reliable in vivo applications. At the application level, advancing the translational potential of polypeptide assembly systems remains a key challenge. Through strategies such as surface modification, biomimetic coating, or integration with other functional materials, their in vivo stability, targeting specificity, and delivery efficiency can be significantly improved. In the future, these materials are expected to play increasingly important roles in diverse fields including drug delivery, tissue regeneration, intelligent biosensing, and green energy storage. Overall, with the maturation of computational design tools, the refinement of in vivo validation platforms, and the strengthening of

interdisciplinary collaboration, polypeptide self-assembled materials are transitioning from experimental exploration toward a new era of controllable design and practical implementation.

Acknowledgments

This work was supported by grants from the National Natural Science Foundation of China (Grant No.31860607), Major Science and Technology Projects in Yunnan Province (Grant No.202202AG050013) and Yunnan Province Science and Technology Department (Grant No.202403AP140003).

Disclosure

The author(s) report no conflicts of interest in this work.

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