http://dx.doi.org/10.1097/mm9.0000000000000007

MedMat

Perspective

OPEN

Peptide–nanomaterial interactions: a key to controlled hierarchical morphology and assembly

Enbo Zhu[a,b,*], Yan-Ruide Li[b], Zeyang Liu[a], Shaolei Wang[a]

1. Introduction

The interactions between biomolecules and nanomaterials have emerged as a pivotal area of research, offering profound implications for the development of hierarchical structures with precise assembly control. At the intersection of nanotechnology, biochemistry, and materials science, this interdisciplinary field explores how biomolecules such as DNA, peptides, and their derivations can direct the synthesis and assembly of nanomaterials into complex, functional architectures and, conversely, how nanomaterials can influence the assembly and organization of biomolecules.

Polypeptides, with their inherent structural sophistication and functional properties, exhibit capabilities such as self-assembly, specific binding, and molecular recognition. These characteristics render them ideal candidates for templating and directing the assembly of nanomaterials. By leveraging the specific interactions between peptides and nanomaterials, researchers can achieve fine control over hierarchical synthesis and assembly processes, resulting in materials with tailored properties and enhanced performance. The hierarchical structuring of materials, where components are organized in a multilevel arrangement from the nanoscale to the macroscale, is essential for attaining advanced functionalities. This approach not only emulates natural processes, where biological systems demonstrate remarkable hierarchical organization, but also paves the way for the creation of novel synthetic systems with unprecedented capabilities.[1–3]

Conversely, nanomaterials can significantly influence the assembly and organization of peptides. The unique physicochemical properties of nanomaterials provide an exceptional platform for the immobilization and manipulation of peptides. This interaction can induce conformational changes in peptides and can be harnessed to investigate fundamental mechanisms that are otherwise challenging to observe in other systems.[4]

In this perspective, we explore biomimetic strategies employed to achieve hierarchical structuring through peptide–nanomaterial interactions. Additionally, we highlight recent advances and key applications of these hybrid systems, illustrating their potential to drive innovative research and development in the future. By providing a comprehensive overview of current methodologies and breakthroughs, this perspective underscores the transformative potential of peptide–nanomaterial interactions in advancing the frontiers of nanotechnology and materials science.

2. Biomimetic methods: learning from nature

Nanostructuring approaches for high-performance materials have transformed the study of functional materials. However, a major challenge remains in achieving precise control over nanostructure synthesis and assembly. Often, this challenge is met through trial and error, employing nonspecific molecules as surfactants due to the difficulty in identifying suitable candidates for directed nanocrystal formation and organization.

In contrast, nature provides simple, efficient strategies to precisely control material structures, yielding superior functions under benign conditions with minimal environmental impact. Notably, most intricate nanoscale structures found in nature are formed under ambient conditions, which remain difficult to replicate through conventional chemical synthesis, even with the control afforded by manipulating temperature and pressure.

The success of nature lies in the molecular recognition capabilities of biomolecules, refined through billions of years of evolution. Among these, proteins and polypeptides are particularly notable for their exceptional functional properties, offering insights into more sustainable and effective approaches for material design.

3. Peptide-assisted nanomaterial hierarchical assembly

By manipulating the conformations and chemical compositions of peptides, nanocrystal formation and assemblies can be controlled hierarchically.[1] For example, using a biomimetic route combined with quantitative simulations, higher-order structures of the peptide T7 (Ac-TLTTLTN-$CONH_2$) have been shown to drive the anisotropic growth and subsequent long-range anisotropic and unidirectional assembly of platinum (Pt) nanocrystals. The ST-turn motif, identified and experimentally validated, plays a crucial role in recognizing Pt{100} facets, leading to the formation of Pt cubes. At higher concentrations, T7 spontaneously transforms from an ST-turn to a β-sheet configuration. This self-assembly process, along with the specific interaction between T7 and cubic Pt nanocrystals, organizes the synthesized Pt nanocrystals into 2D sheets comprising unidirectional 1D assemblies along the [100] direction, extending over tens of micrometers (Figure 1A).

[a]Department of Bioengineering, UCLA, Los Angeles, California, USA, [b]Department of Microbiology, Immunology & Molecular Genetics, UCLA, Los Angeles, California, USA.

**Corresponding author: Address: Enbo Zhu, Department of Bioengineering, UCLA, 410 Westwood Plaza, Los Angeles, CA 90095, USA. E-mail address: enbozhu@ucla.edu (E. Zhu).*

MedMat (2024) 1:2

Received: 31 July 2024; Accepted 17 September 2024

Published online 25 September 2024

4. Peptide hierarchical assembly on nanomaterial surface

On the other hand, the behavior of peptides, including their configuration, assembly, and movement, is influenced by the material surfaces they contact. For instance, T7 peptides were found to spontaneously adopt ST-turn structures on the Pt{100} facet of Pt nanocubes.[1] The growth of 1D peptide crystals in rows on crystalline substrates has been reported, with these rows subsequently assembling laterally into films and ultimately forming 2D arrays. This process was investigated using molecularly resolved in situ atomic force microscopy, and the results were compared to molecular dynamics (MD) simulations. The findings revealed that the arrays assembled one row at a time, with the nuclei being ordered from the earliest stages and forming without a free energy barrier or critical size. The results verify long-standing but unproven predictions of classical nucleation theory in 1D while revealing key interactions underlying 2D assembly[4] (Figure 1B).

5. Applications of peptide–nanomaterial complexes

The rational design of peptide–nanomaterial complexes can enhance performance across multiple disciplines, including catalysis,[2,3] biomedicine,[6,7] and electronics.[8] For example, peptides can introduce grain boundaries in Pt nanostructures, enhancing oxygen reduction reaction activity, which demonstrates the potential of these engineered materials in catalytic applications.[2,3] Additionally, precise control over the shape and size of self-assembled peptide nanomaterials enables the creation of biologically inspired structures with diverse functions, including targeted transport at the subcellular level.[6,7] In electronics, peptide-based nanomaterials have attracted growing interest as novel charge transport materials due to their exceptional electrical properties and intrinsic biocompatibility, making them a compelling choice for bioelectronic applications.[8]

6. Methods in peptide–nanomaterial interaction research

Display techniques, including phage and mRNA display, can be used to select peptides with specific recognition. Phage display involves expressing a library of peptide variants on phage virions, linking each variant to its encoding DNA, and selecting based on binding affinity through panning. This process involves incubating phage-displayed peptides with a target-coated plate, washing away unbound phage, and eluting bound phage, followed by amplification and additional rounds to enrich binding sequences. DNA sequencing then identifies clones, which are analyzed for properties such as hydrophobicity, side-chain length, and functional group similarities. If no patterns emerge, further biopanning rounds are conducted.[1–3] Compared to phage display, mRNA display is more technically challenging but superior in peptide selection, with a higher probability of selecting rare sequences and greater diversity. mRNA display involves in vitro creation and selection of a library much larger than phage display, in a purely monovalent format, and with encoded libraries directly amenable to high throughput sequencing for structure-activity analysis[9] (Figure 1C).

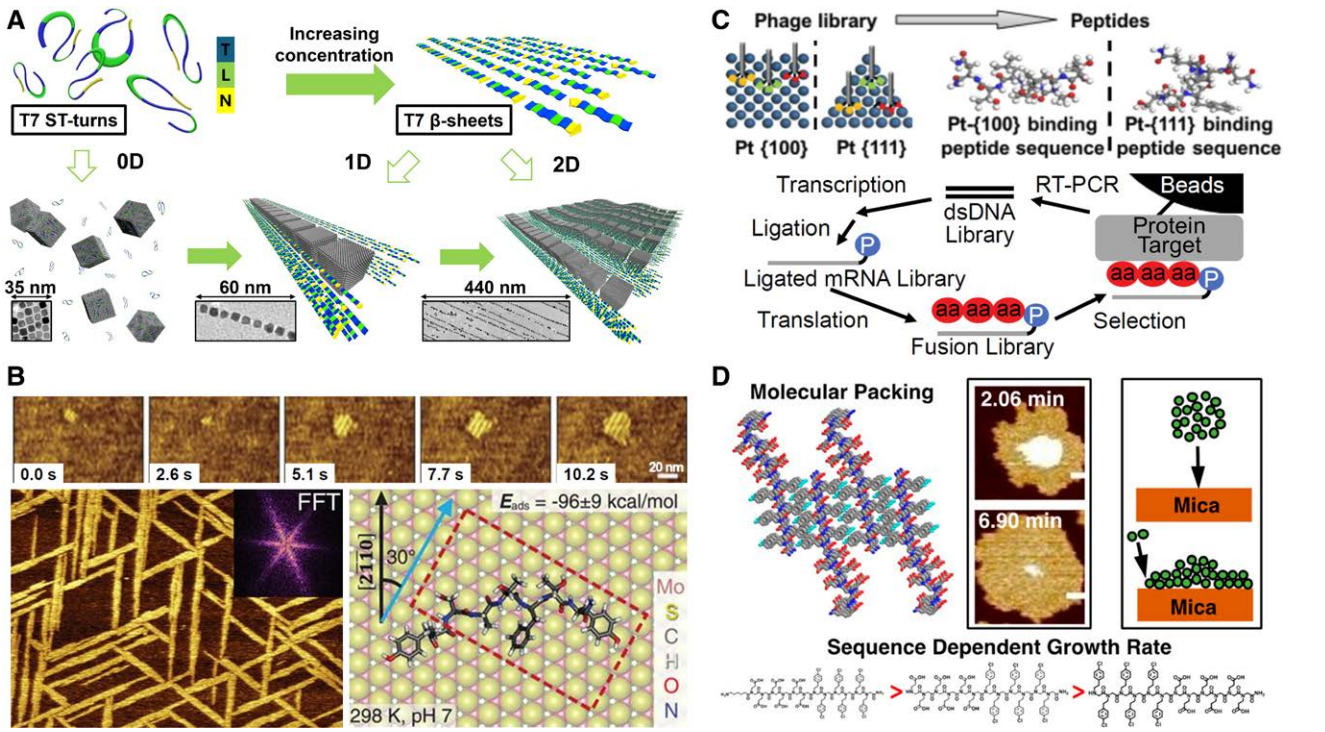

Figure 1. Interactions of nanomaterials with peptides and peptoids for controlled hierarchical morphology and assembly. (A) The behavior of nanomaterials can be controlled by peptides. For example, molecular changes in T7 peptides drive the hierarchical organization of platinum (Pt) cubic nanocrystals. Reproduced with permission from Zhu et al[1] Copyright © 2019 American Chemical Society. (B) Conversely, peptides can be regulated by nanomaterials. The MoSBP1 peptide assembles on 2D MoS2 surfaces at preferred angles, demonstrating a bidirectional interaction. Reproduced with permission from Chen et al[4] Copyright © 2018, American Association for the Advancement of Science. (C) Phage display and mRNA display techniques are utilized for the selection of peptides, allowing for targeted interactions and enhanced assembly processes. (D) Influence of peptoid sequence on the mechanisms and kinetics of 2D assembly. Reproduced under the terms of a Creative Commons Attribution 4.0 Unported License.[5] Copyright © 2024, The Authors.

Many techniques are involved in characterizing peptide–nanomaterial interactions.[10] Chromatographic methods, such as high-performance liquid chromatography, are employed to separate and quantify peptides. Spectroscopic methods, including ultraviolet-visible spectroscopy, Fourier transform infrared spectroscopy, Raman spectroscopy, and nuclear magnetic resonance Spectroscopy, provide structural information about the peptides.[1] Microscopic techniques, such as transmission electron microscopy, scanning electron microscopy, and atomic force microscopy, reveal the morphology of both peptides and nanomaterials.[1,4] Notably, atomic force imaging and spectroscopy offer unique tools for investigating molecular interactions and dynamics in biomolecular and biomineral systems in situ and therefore are increasingly utilized in studying peptide–nanomaterial interactions[4,11] (Figure 1B). Besides experimental methods, simulation methods are also important. MD simulation has become a reliable tool to gain insight into the details of molecular motion, nanoscale assembly, and crystal growth, where the interpretability of the force field parameters is essential to explain and predict the physical and chemical behavior.[12]

7. Peptoid: peptide derivation with unique properties

However, the higher-order structures formed in peptides can sometimes pose significant challenges. The side-chain chemistry of amino acid residues, combined with the stereostructure formed by hydrogen bonds, creates intricate and tangled relationships that are difficult to investigate comprehensively in mechanism studies and structure design. Additionally, peptide bonds in peptides exhibit low stability and are highly susceptible to proteolytic degradation. This inherent instability and complexity can hinder the design and application of peptide-based strategies, necessitating alternative approaches for more robust and controllable systems.

Peptoids, which are a type of sequence-defined peptide mimetic, are particularly attractive for this purpose, because they are easy to synthesize and exhibit low structural complexity, extensive side-chain diversity, and high stability. Unlike peptides and proteins, peptoids lack backbone hydrogen bond donors; thus they offer unique opportunities for tuning intermolecular and molecule–particle interactions solely through the variation of side-chain chemistry. They have already proven to be a promising class of ligands for controlling inorganic crystal formation.

To this end, peptoids, which are sequence-defined peptide mimetics, present a highly attractive solution due to their ease of synthesis, simplified structural complexity, extensive side-chain diversity, and remarkable stability. Unlike peptides and proteins, peptoids lack backbone hydrogen bond donors, which allows for unique opportunities to tune intermolecular and molecule–particle interactions solely through the variation of side-chain chemistry. This distinctive feature enhances their versatility and control in various applications. Recently, peptoids have been identified as effective ligands for directing nanomaterial formation and assembly,[13] and they have demonstrated the ability to self-assemble on material surfaces,[5] further expanding their potential in developing new functional nanomaterials for a range of applications.

The effect of peptoid sequence on the mechanism and kinetics of 2D assembly on mica surfaces was studied.[5] The results show that peptoid assembly on mica begins with aggregates forming 2D islands that grow by attaching monomers or small oligomers. Differences in growth rate and solubility are sequence dependent. The sequence with the slowest growth rate in bulk and the highest solubility shows almost no detachment. Furthermore, a peptoid sequence with a hydrophobic tail conjugated to the final carboxyl residue in the hydrophilic block exhibits enhanced hydrophobic interactions and rapid assembly both in bulk and on mica. These findings suggest that, although π–π interactions are crucial for assembly, sequence details and substrate interactions significantly affect stability and kinetics (Figure 1D).

8. Challenges and perspectives

Despite promising advancements in peptide–nanomaterial interactions for hierarchical morphology and assembly, several challenges remain. Addressing these can lead to future innovations and impactful applications.

A key challenge lies in the precise control of peptide sequences and structures, which is essential due to the complex nature of peptide–nanomaterial interactions. While peptide selection and design often rely on display techniques, their effectiveness can be limited. However, advancements in high-resolution microscopy, simulation, and machine learning offer opportunities to enhance peptide design, fostering more efficient and targeted assembly processes.[10]

Another significant hurdle is the susceptibility of peptides to protease degradation, compromising their stability and functionality. Solutions such as peptide mimetics (eg, peptoids) and chemical modifications are being explored to improve stability, particularly under harsh conditions.

Scalability and reproducibility pose further challenges. Methods effective in controlled, small-scale environments often struggle to transition to industrial applications. Robust, scalable approaches for peptide-assisted nanomaterial synthesis and assembly are critical to bridge this gap.

Additionally, integrating these nanostructures into functional devices without compromising their properties presents a complex task. To address these challenges, interdisciplinary collaboration is essential, involving biochemistry, materials science, nanotechnology, and engineering.

Finally, long-term biocompatibility must be ensured for applications in biomedical fields,[6,7] adding another layer of complexity to the scalability and reproducibility of peptide–nanomaterial systems.

Acknowledgments

E.Z. acknowledges Dr. Yu Huang for her guidance on related studies.

Conflicts of interests

The authors declare that they have no conflicts of interest.

Author contributions

E.Z. conceived, organized, and wrote the manuscript. All authors revised the manuscript. All authors discussed and approved the final manuscript.

References

[1] Zhu E, Wang S, Yan X, et al. Long-range hierarchical nanocrystal assembly driven by molecular structural transformation. *J Am Chem Soc*. 2019;141(4):1498–1505.

[2] Zhu E, Liu Y, Huang J, et al. Bubble-mediated large-scale hierarchical assembly of ultrathin Pt nanowire network monolayer at gas/liquid interfaces. *ACS Nano*. 2023;17(14):14152–14160.

[3] Zhu E, Xue W, Wang S, et al. Enhancement of oxygen reduction reaction activity by grain boundaries in platinum nanostructures. *Nano Res*. 2020;13(12):3310–3314.

[4] Chen J, Zhu E, Liu J, et al. Building two-dimensional materials one row at a time: avoiding the nucleation barrier. *Science*. 2018;362(6419):1135–1139.

[5] Yadav Schmid S, Ma X, Hammons JA, et al. Influence of peptoid sequence on the mechanisms and kinetics of 2D assembly. *ACS Nano*. 2024;18(4):3497–3508.

[6] Wang Y, Zhan J, Huang J, et al. Dynamic responsiveness of self-assembling peptide-based nano-drug systems. *Interdiscip Med*. 2023;1(1):e20220005.

[7] An H-W, Mamuti M, Wang X, et al. Rationally designed modular drug delivery platform based on intracellular peptide self-assembly. *Exploration (Beijing, China)*. 2021;1(2):20210153.

[8] Zhao J, Liu Q, Tong X, et al. Rational design of bio-inspired peptide electronic materials toward bionanotechnology: strategies and applications. *Adv Funct Mater*. 2024;34(29):2401466.

[9] Millward SW, Takahashi TT, Roberts RW. A general route for post-translational cyclization of mRNA display libraries. *J Am Chem Soc*. 2005;127(41):14142–14143.

[10] Cai X, Xu W, Ren C, et al. Recent progress in quantitative analysis of self-assembled peptides. *Exploration (Beijing, China)*. 2024;4(4):20230064.

[11] De Yoreo JJ, Chung S, Friddle RW. In situ atomic force microscopy as a tool for investigating interactions and assembly dynamics in biomolecular and biomineral systems. *Adv Funct Mater*. 2013;23(20):2525–2538.

[12] Liu J, Zeng J, Zhu C, et al. Interpretable molecular models for molybdenum disulfide and insight into selective peptide recognition. *Chem Sci*. 2020;11(33):8708–8722.

[13] Jin B, Yan F, Qi X, et al. Peptoid-directed formation of five-fold twinned Au nanostars through particle attachment and facet stabilization. *Angew Chem*. 2022;134(14):e202201980.

How to cite this article: Zhu E, Li Y-R, Liu Z, Wang S. Peptide–nanomaterial interactions: a key to controlled hierarchical morphology and assembly. MedMat 2024;1(2):e00007. doi: 10.1097/mm9.0000000000000007