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LETTER TO THE EDITOR

# Nature-inspired supramolecular assemblies for precise biomedical imaging and therapy



## KEY WORDS

Supramolecular assembly;  
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## To the editor:

The precise diagnosis and effective therapy of refractory diseases, such as neurodegenerative diseases, coronary heart diseases and cancers, is critical to increase the survival rate and improve the life quality of patients. Most of the conventional small molecular medicines are heavily associated with the limitations of poor solubility, low targeting efficiency, inducing drug resistance and systemic toxicity, promoting scientists to develop new strategies for overcoming these limitations. Supramolecular assembly is based on the intermolecular interactions, including van der Waals force, electrostatic attraction,  $\pi$ - $\pi$  interaction and hydrophobic interaction, in which the disordered building blocks are linked together to form ordered architectures. In contrast to covalently bonded molecular structure, weak noncovalent interactions endow supramolecular assemblies with highly flexible tunability, reversibility and dynamic-responsiveness. Supramolecular assemblies are widely observed in natural living systems, such as double-strand DNA, phospholipid membranes, ribosomes, exosomes, protein folding, playing vital roles in various biological functions. Inspired by the supramolecular structures in nature, scientists have been devoted to developing artificial supramolecular assemblies, which have gained increasing influence in biomedical applications (Fig. 1)<sup>1,2</sup>.

Diagnostic and therapeutic agents can be readily integrated with supramolecular building blocks without tedious organic

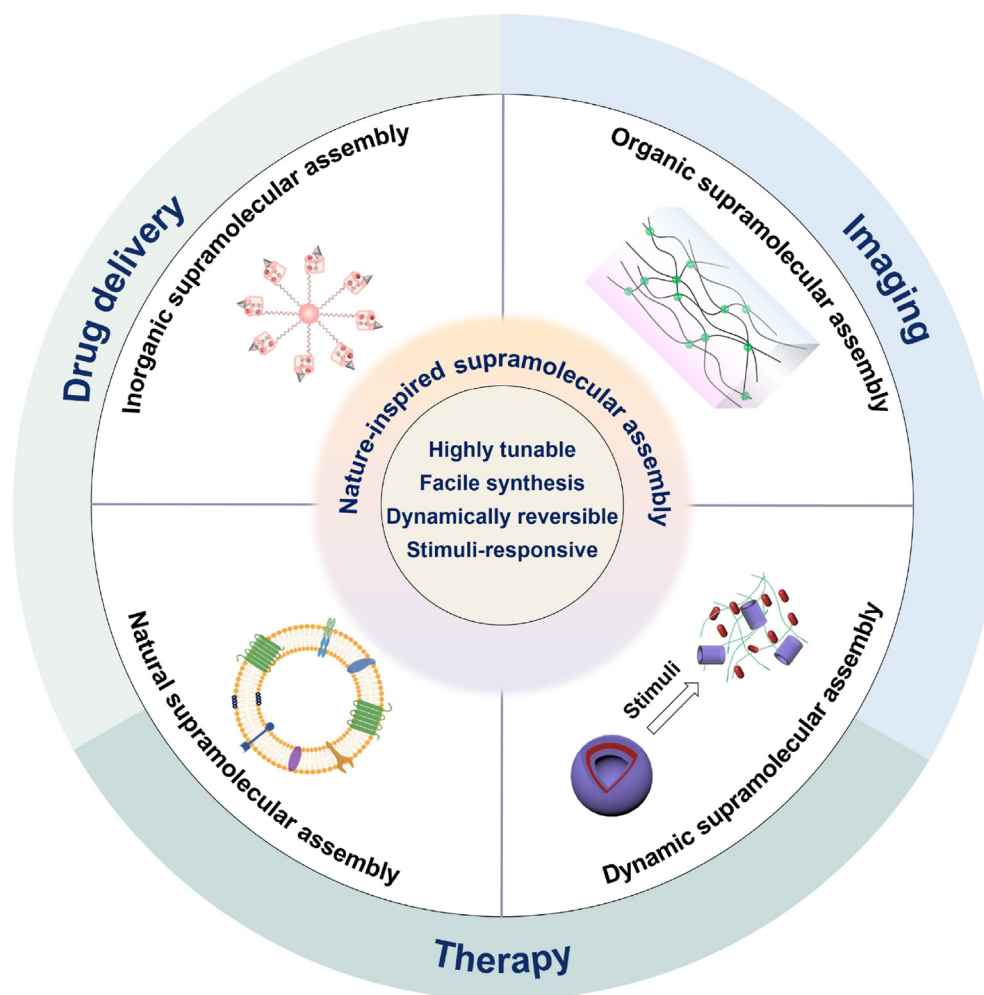
synthesis. By taking advantage of supramolecular strategy, some issues that hinder the clinical applications of conventional theranostic agents can be efficiently solved. For example, the solubility and stability of small molecule therapeutic agents, *e.g.*, paclitaxel, can be unprecedentedly improved by supramolecular containers through host-guest interactions. Moreover, supramolecular-based surface-engineering strategy can significantly improve disease-targeted imaging performance of nanoparticle-based diagnostic agents. For instance, our group designed a supramolecular container-based surface-engineering approach for biological targeting, where the orientation of targeting ligands on the nanoparticle surface was precisely controlled through the bilateral host-guest interaction between an acyclic cucurbituril (aCB) molecular and spermidine<sup>3</sup>. The functional imaging probes were immobilized with tumor targeting ligands *via* a noncovalent manner by using supramolecular container aCB, which ensured full exposure of the bioactive moieties of the targeting ligands, thus resulting in enhanced tumor targeting and imaging efficiency.

In addition to serving as drug carriers or surface modification, various organic supramolecular assemblies have been developed for straightforward disease treatment. For example, Wang et al.<sup>4</sup> constructed a supramolecular nanotube hydrogel comprised of a peptide-drug conjugate and STING agonist for cancer chemoimmunotherapy. The supramolecular nanotube hydrogel enabled tumors to be more sensitive to immunotherapies, which could significantly augment antitumor immune responses in a safe way. Moreover, supramolecular polymers with tunable signal intensity and flexible geometry are also promising candidates for the signaling of cells. Recently, Álvarez et al.<sup>5</sup> reported supramolecular scaffolds of nanoscale fibrils containing two distinct biological signals to promote functional recovery of severe spinal cord injury. By slightly mutating the peptide sequence of the inactive domains, the biological responses of cells *in vitro* and functional recovery of mice *in vivo* were significantly improved.

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**Figure 1** Schematic illustration of the nature-inspired supramolecular assemblies with multiple advantages for various biomedical applications.

The weak and reversible intermolecular interactions endow supramolecular assemblies with highly sensitive stimuli-responsiveness. The rationally designed stimuli-responsive supramolecular assemblies undergo structural changes once exposed to endogenous stimuli [*e.g.*, glutathione (GSH), pH, enzyme and hypoxia] or exogenous stimuli (*e.g.*, thermo, light and magnetic field), leading to the controlled drug release and the activation of theranostic functions. Recently, Cheng et al.<sup>6</sup> developed a mitochondria-targeting supramolecular assembly with triple stimuli-responsiveness to irradiation, acidity and GSH, realizing superior anti-cancer performance due to the tumor-responsive disassembly, accelerated drug release and combinational therapy. Furthermore, Jiang et al.<sup>7</sup> fabricated a supramolecular vesicle that is responsive to five stimuli (pH, CO<sub>2</sub>, GSH, Zn<sup>2+</sup> and hexanediamine) to meet various controlled drug release requirements. The stimuli-responsive supramolecular assemblies that can achieve specific and controllable functional activation at the disease site have great application prospects in the precise diagnosis and treatment of refractory diseases.

In parallel with the development of artificial supramolecular architectures, natural supramolecular assemblies, such as exosomes, have also been widely explored for biomedical applications. Exosome is a kind of lipid bilayer-encapsulated

extracellular vesicle originating from endosome, which plays an important role in cellular communication processes in the body<sup>8</sup>. Benefiting from their excellent biocompatibility, long circulation time, and tumor targeting capability, exosomes show great promise in drug delivery and cancer therapy. Kamerkar et al.<sup>9</sup> engineered the exosomes originating from normal fibroblast-like mesenchymal cells to deliver short interfering RNA or hairpin RNA for pancreatic cancer treatment, which facilitated specific targeting of oncogenic KRAS and improved overall survival. In addition, exosomes can elicit robust immune responses against cancer. By artificially engineering exosomes, tumor-associated antigen delivery or immunostimulatory pathway engagement could be realized in lymphoid and myeloid cells. Further attention and study should be given to exosome-mediated immunoregulation. This emerging research field may potentially decipher other mechanisms of cancer aggressiveness, providing a new avenue for cancer treatment.

Over the past few decades, by learning from supramolecular assemblies in nature, impressive achievements have been made in biomedical imaging and therapy. Despite of the progression, there are challenges remained to be addressed for further clinical application. Firstly, just as a coin has two sides, the supramolecular system may dissociate during the *in vivo* circulation due to the relatively weak noncovalent interaction, leading to

undesired leakage of diagnostic agents or therapeutic drugs. Therefore, continues efforts should be made to design more dynamically controllable supramolecular assembly platforms with on-demand drug release and functional activation. Secondly, the precisely controlled structure of natural supramolecular assemblies is the key to exerting their biological functions in living systems. Thus, by learning from nature, atomically precise engineered supramolecular assemblies are worth in-depth investigation to obtain high-performance artificial materials. Furthermore, the safety and toxicological issues of the supramolecular assemblies should be systemically evaluated with standardized and authoritative methods for further clinical trials. More intensive studies regarding the supramolecular assembly of natural substances, such as exosomes, polypeptides, proteins, and nucleic acids, are encouraged, for the merit of minimizing side effects and toxicity.

In conclusion, owing to the highly-ordered, flexible and tunable structures, supramolecular assemblies in living biological systems, such as DNA, proteins, and phospholipid membranes, are involved in precisely regulating life activities in nature. Mimicking supramolecular architectures from nature opens a promising avenue to develop biomimetic materials with biological activity close to natural substances, which shall eventually achieve highly precise diagnosis and therapy.

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#### Conflicts of interest

The authors have no conflicts of interest to declare.

#### References

1. An HW, Mamuti M, Wang X, Yao H, Wang MD, Zhao L, et al. Rationally designed modular drug delivery platform based on intracellular peptide self-assembly. *Exploration* 2021;1:20210153.

2. Liu Y, Liu CZ, Wang ZK, Zhou W, Wang H, Zhang YC, et al. Supramolecular organic frameworks improve the safety of clinically used porphyrin photodynamic agents and maintain their antitumor efficacy. *Biomaterials* 2022;284:121467.
3. Zhao M, Liang Z, Zhang B, Wang Q, Lee J, Li F, et al. Supramolecular container-mediated surface engineering approach for regulating the biological targeting effect of nanoparticles. *Nano Lett* 2020;20:7941–7.
4. Wang F, Su H, Xu D, Dai W, Zhang W, Wang Z, et al. Tumour sensitization via the extended intratumoural release of a STING agonist and camptothecin from a self-assembled hydrogel. *Nat Biomed Eng* 2020;4:1090–101.
5. Álvarez Z, Kolberg-Edelbrock AN, Sasselli IR, Ortega JA, Qiu R, Syrgiannis Z, et al. Bioactive scaffolds with enhanced supramolecular motion promote recovery from spinal cord injury. *Science* 2021;374:848–56.
6. Cheng Y, Ji Y, Tong J. Triple stimuli-responsive supramolecular nanoassembly with mitochondrial targetability for chemophotothermal therapy. *J Control Release* 2020;327:35–49.
7. Jiang L, Huang X, Chen D, Yan H, Li X, Du X. Supramolecular vesicles coassembled from disulfide-linked benzimidazolium amphiphiles and carboxylate-substituted pillar[6]arenes that are responsive to five stimuli. *Angew Chem Int Ed* 2017;56:2655–9.
8. Kugeratski FG, Hodge K, Lilla S, McAndrews KM, Zhou X, Hwang RF, et al. Quantitative proteomics identifies the core proteome of exosomes with syntenin-1 as the highest abundant protein and a putative universal biomarker. *Nat Cell Biol* 2021;23:631–41.
9. Kamerkar S, LeBleu VS, Sugimoto H, Yang S, Ruvivo CF, Melo SA, et al. Exosomes facilitate therapeutic targeting of oncogenic KRAS in pancreatic cancer. *Nature* 2017;546:498–503.

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