Customizable metal-phenolic supraparticles based on rationally designed building blocks

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Abstract

Metal-phenolic networks (MPNs) as a versatile platform for particle engineering have been well developed due to their integrated benefits of both metal ions and phenolic molecules. However, the approaches to broaden their applications are limited due to the single-driving force from the coordination of these two components. Herein, we developed a universal approach to introducing programmable assembles into MPNs to form metal-phenolic supraparticles based on the rationally designed phenolic building blocks. These as-prepared building blocks can first assemble into primary nanoparticles driven by various controllable intermolecular interactions (i.e., metal-organic coordination, host-guest interaction, and hydrophobic interaction), followed by particle assembly with metal ions to coat on different templates. The introduction of multiple assembly modalities into phenolic building blocks enriches the functionalities of these metal-phenolic supraparticles, such as dual-pH responsibility, light-controllable permeability, and rapid fluorescence labeling of living cells. Our work provides a conceptual and practical paradigm for customizing MPNs with hierarchical structures by importing various assembly strategies via rationally designed phenolic building blocks.

Keywords: metal-phenolic supraparticles, function customization, rational design, phenolic building blocks
**Introduction**

Metal-phenolic networks (MPNs), an emerging class of metal-organic supramolecular assemblies formed through coordination chemistry, can be rapidly deposited on a broad range of substrates, including organic, inorganic, hybrid, and living cells.\textsuperscript{1–4} Owing to their facile preparation, universal adhesion, pH responsiveness, biocompatibility, and modular composition, MPNs have attracted extensive attention in numerous fields.\textsuperscript{5–10} Generally, the constructed MPN assemblies can integrate the properties of each modular composition (i.e. phenolic molecules and metal ions) to determine the physicochemical properties, structures, and functionalities, which further enable their tailorability for diverse applications.\textsuperscript{11–15} Currently, strategies have been explored to impart additional novel properties to MPNs by covalently tethering functional polymers into phenolic molecules.\textsuperscript{16–18} However, these modification strategies did not alter the fundamental of the assembly formation via the metal-driven coordination of phenolic groups. From a fundamental perspective, the single driving force of coordination can only lead to the formation of assemblies with a primary-level nanostructure, hampering the further development of MPNs in structural and functional complexity.

Our recent studies showed that the metal-driven coordination of phenolic moieties can facilitate an interfacial assembly of colloidal building blocks on the secondary substrates.\textsuperscript{19} This polyphenol-based modular approach provides a versatile platform for the construction of complex functional supraparticles, therapeutically engineered cells, and photo-driven biohybrids for chemical production.\textsuperscript{19–21} These previous studies inspired us about the possibility of designing complex functional metal-phenolic supraparticles through the programmable assembly from synthetic phenolic building blocks to their primary nanoparticles, possessing high dimensional control of structural and functional diversities.

Here, we explore a universal platform for building customizable metal-phenolic supraparticles by integrating controlled self-assembly strategies based on rationally designed phenolic building blocks (Figure 1). Specifically, dopamine, a representative phenolic (catechol) molecule, was first covalently coupled with orthogonal functional groups, including pyridine (Py), azophenyl (Azo), and long-chain alkane (Ole) groups, to form rationally designed phenolic building blocks, which enables the first assembly into primary nanoparticles (Figure 1A). These primary nanoparticles are capable of performing modular assembly to customizable metal-phenolic supraparticles, including \([\text{Cat}_{\text{Py}}-\text{Pd}^{II}] - \text{Zn}^{II}\), \([\text{Cat}_{\text{Azo}}-\text{PCD}] - \text{Fe}^{III}\), and \([\text{Cat}_{\text{Ole}}-X] - \text{Fe}^{III}\) with a selection of orthogonal functional groups, cargo molecules, and assembling metal ions (the parentheses refer to the name of each primary nanoparticle, which is explained in ‘Supplementary Section 1.6, nomenclature of metal-phenolic supraparticles’) (Figure 1B). These combinations of different levels of building blocks enable a range of functionalities such as base-stimuli dissociation, light-stimuli disassembly, and locking fluorescent dyes. Our results showed the broadened functionalities of MPNs, such as acid/base dual-responsive dissociation (Figure 1C), UV/Vis dual-responsive permeability (Figure 1D), and rapid fluorescence labeling of living cells (Figure 1E). This study enables the individual customization of MPNs, which may be of broad interest in various applications, such as catalysis, smart drug delivery, and cell-based therapies.
Figure 1. Construction of customizable metal-phenolic supraparticles through the sequential assembly of rationally designed building blocks. (A) Schematic illustration of the preparation of primary nanoparticles (CatPy-PdII, CatAzo-PCD, and CatOle-X) through both the amidation strategy based on the representative phenolic molecule dopamine and ligands I (isonicotinoyl chloride, 4-phenylazobenzoyl chloride, and oleoyl chloride) and intermolecular interactions between rationally designed building blocks and ligands II (PdII ions, polycyclodextrin (PCD), and hydrophobic cargo molecule “X”). (B) Modular assembly of metal-phenolic supraparticles with a selection of versatile modularized primary nanoparticles, templates, and metal ions. (C) Acid/base dual-responsive dissociation of [CatPy-PdII]-ZnII capsules endowed by phenolic group and pyridine structure in CatPy. (D) UV/Vis dual-responsive controlled permeability of [CatAzo-PCD]-FeIII capsules based on host-guest interaction between azobenzene structure of CatAzo and PCD. (E) Polyphenol-mediated rapid assembly of CatOle and FeIII on cells for rapid fluorescence labeling of living cells ([CatOle-X]-FeIII).
Preparation and modular assembly of primary nanoparticles

We first synthesized the ligands I-modified dopamine as the rationally designed building blocks by the amidation strategy: N-(3,4-dihydroxyphenethyl)isonicotinamide (CatPy), (E)-N-(3,4-dihydroxyphenethyl)-4-(phenyl diazenyl)benzamide (CatAzo), and (Z)-N-[2-(3,4-dihydroxyphenyl)ethyl]-9-octadecenamide (CatOle), respectively (Figure 1A, Supplementary Figure S1). Their chemical structures and molecular weights were determined by proton nuclear magnetic resonance (1H NMR) spectroscopy, carbon-13 nuclear magnetic resonance (13C NMR) spectroscopy, and quadrupole time-of-flight mass spectrometry (Q-TOF-MS) (Supplementary Figures S2–S5); the characterization data were provided in Section S1.3. Subsequently, these designed phenolic building blocks (CatPy, CatAzo, and CatOle) were rapidly assembled with ligands II (PdII ions, polycyclodextrin (PCD), and hydrophobic cargo molecule “X”) via different intermolecular interactions (coordination, host-guest, and hydrophobic interaction) to construct CatPy-PdII, CatAzo-PCD, and CatOle-X primary nanoparticles (Figure 1A, Supplementary Section S1.4). Coumarin 6 (C6) was selected as a representative hydrophobic cargo molecule for further assembly characterization. The formation of CatPy-PdII, CatAzo-PCD, and CatOle-C6 particles can be clearly observed from the photographs of the centrifuged sample solutions, and their size distribution (~100 nm) was further measured by the dynamic light scattering (DLS) (Supplementary Figure S6). Intriguingly, the obtained nanoparticles can subsequently coordinate with metal ions (ZnII or FeIII) to coat and functionalize templates to form [CatPy-PdII]-ZnII capsules, [CatAzo-PCD]-FeIII capsules, and [CatOle-X]-FeIII-coated cell biohybrids (Figure 1B, Supplementary Section S1.5–S1.7). Photographs and the zeta potential values of sample solutions before and after [CatPy-PdII]-ZnII, [CatAzo-PCD]-FeIII, and [CatOle-X]-FeIII coating templates preliminarily demonstrated the successful assembly of primary nanoparticles on templates (Supplementary Figure S7). Divalent-metal-ion (ZnII)-chelated CatPy existed transition absorption peaks of CatPy ligand in UV/Vis spectroscopy, proving the coordination of CatPy-ZnII (Supplementary Figure S8A).22 Meanwhile, the coordination in both CatPy-FeIII and CatOle-FeIII was also further confirmed by UV/Vis spectroscopy with the presence of the ligand-to-metal charge-transfer band from 400 to 600 nm (Supplementary Figures S8B and S8C).12,23

Acid/base dual-responsive dissociation of [CatPy-PdII]-ZnII capsules

Dynamic MPN materials that can respond to pH stimuli have attracted interest in the area of biomedical and materials science. Currently, although the multivalent coordination property of MPN materials allows capsules to disassemble in specific acidic conditions (e.g., pH < 4.0 for FeIII-TA capsules), MPNs have not yet been engineered to respond to alkaline stimuli, thus lacking the capability to respond to complex microenvironments in nature.24–27 CatPy-PdII primary nanoparticles combined the acid-responsiveness of polyphenols with the base-responsiveness of pyridine as the dual-responsive [CatPy-PdII]-ZnII capsules, which can dissociate under either acid or base conditions. Transmission electron microscopy (TEM) revealed that the average
diameter of the CatPy-PdII particles was about 100 nm, which was consistent with the DLS analysis (Figure 2A). [CatPy-PdII]ZnII capsules were fabricated by mixing CatPy-PdII and ZnII ions solutions in the presence of calcium carbonate (CaCO3) templates (Supplementary Section S1.7). As observed by scanning electron microscopy (SEM, Figure 2A), the rough surface of the CaCO3 particles confirmed the presence of the coated [CatPy-PdII]-ZnII. Compared with the SEM images of adding only the same concentration of ZnII or PdII ions, [CatPy-PdII]-ZnII-coated CaCO3 surface formed more homogeneous and compact particles (Figure 2A, Supplementary Figure S9), validating the effectiveness of sequential assembly. The monodisperse spherical [CatPy-PdII]-ZnII capsules observed from bright-field microscopy images highlighted the stability of the free-standing networks after the template removal (Figure 2A). Energy-dispersive X-ray (EDX) mapping demonstrated the presence of Zn and Pd elements on the CaCO3 template (Figure 2B).

To confirm the coordination of CatPy and metal ions (ZnII and PdII), X-ray photoelectron spectroscopy (XPS) analysis was performed on the [CatPy-PdII]-ZnII complex (Supplementary Figures S10A–S10D). Specifically, the typical double peaks of Pd were clearly observed at binding energies of 338.38 and 343.68 eV, corresponding to Pd 3d3/2 and Pd 3d5/2, respectively. The Zn 2p core level spectrum showed two peaks appearing at 1045.68 and 1022.48 eV with a characteristic peak separation of 23.2 eV, revealing the existence of ZnII. In the O 1s region of the XPS spectra, the HO‒C group of CatPy shifts from 533.6 eV to higher binding energy of 535.1 eV after ZnII chelation, suggesting electron transfer from CatPy to ZnII. Similarly, the N 1s XPS spectra indicated that PdII ions coordinated with CatPy through sharing the electron pair of the pyridine N group. The electron-donating effect from N to metal ions resulted in an appreciable shift of the N 1s binding energy to a higher value. Furthermore, the covalent binding of pyridine and PdII ions was further assessed using Fourier transform infrared (FT-IR) spectrometry (Supplementary Figure S11). Compared with the spectrum of the free pyridine, a new absorption peak appeared at 487 cm⁻¹ in the spectrum of the Pyridine-PdII complex due to the Pd–N stretching vibration. The red shifts of pyridine skeleton vibration bands (i.e., 1601–1560 cm⁻¹ and 1730–1705 cm⁻¹) also suggested the formation of coordination bonds between pyridine and PdII ions.

To demonstrate the dual responsiveness of the [CatPy-PdII]-ZnII capsules in acid-base conditions, the capsules were first incubated under a physiological pH 7.4 solution and then triggered by hydrochloric acid (HCl) solution (pH 3.0 to 6.0) or sodium hydroxide (NaOH) solution (pH 8.0 to 10.0) (Supplementary Section S1.8). After incubation of the capsules at pH 3.0 for 5 h, 56% of the capsules were dissociated compared with those at pH 10.0 (Figures 2C and 2D), suggesting that the ZnII ions and polyphenol in [CatPy-PdII]-ZnII suffered coordination dissociation when the concentration of H⁺ in solution increased (due to protonation, Figure 2G). Concurrently, after 5 h at pH 10.0, the number of remaining capsules dropped below 23% (Figures 2C and 2D), suggesting that the CatPy-PdII in [CatPy-PdII]-ZnII dissociated when a critical percentage of pyridine was hydrolyzed (Figure 2G). The heat map in Figure 2D showed the relationship between pH and the percentage of remaining capsules, and
it can be found that either increasing or decreasing pH reduced the remaining rate of capsules. As pH-responsive coordination was a characteristic property of MPNs and aromatic N-containing ligand pyridine can coordinate with Pd\textsuperscript{II} ions in acidic aqueous solution (pH 2.0–7.0), the dissociation of Pyridine-Pd\textsuperscript{II} complex under alkaline conditions was further explored by adding Pd\textsuperscript{II} ions to the free pyridine ligand solution.\textsuperscript{24–27,34} After the addition of Pd\textsuperscript{II} ions, the colorless pyridine solution immediately changed to brownish-yellow, suggesting the coordination of pyridine and Pd\textsuperscript{II} ions (Figure 2E). Further, with increasing the OH\textsuperscript{−} concentration in the above solution, the brownish-yellow suspension became clear immediately, indicating the coordination dissociation of pyridine and Pd\textsuperscript{II} ions (Figure 2E). Meanwhile, we characterized the pH-dependent reversible complexation of pyridine and Pd\textsuperscript{II} ions using high-performance liquid chromatography (HPLC, Figure 2F). Considering the instability of isonicotinic acid chloride in water, the coordination dissociation of pyridine from Pd\textsuperscript{II} ions was investigated with isonicotinic acid as the representative pyridine ligand (Supplementary Section S1.9). From the HPLC spectrum of the free pyridine (Figure 2F), a single peak (2.041 min) was generated for free pyridine. After the addition of the Pd\textsuperscript{II} ions solution, significant shifts in the retention time and peak shapes were observed (Figure 2F). The Pyridine-Pd\textsuperscript{II} complex resulted in distinct peaks, corresponding to the disappearance of the free individual pyridine ligand peak (2.410 min) and the appearance of the Pyridine-Pd\textsuperscript{II} complex peak (4.860 min), which indicated a general complexation between pyridine and Pd\textsuperscript{II} ions. To further explore the pH-dependent reversibility of the Pyridine-Pd\textsuperscript{II} complex, the solution was continuously alkalized to 10.0 and it was found that the peaks assigned to the Pyridine-Pd\textsuperscript{II} complex dramatically decreased, while the peaks attributed to the free individual pyridine reappeared (Figure 2F). In addition, the coordination of pyridine with Pd\textsuperscript{II} ions was also demonstrated again by the gradual decrease in the concentration of free pyridine in the supernatant, as shown by the HPLC spectrum of the free pyridine remaining in the supernatant after the combination of pyridine and Pd\textsuperscript{II} ions centrifugation (Supplementary Figures S12 and S13A). Correspondingly, with the addition of NaOH solution, the concentration value of the free pyridine in the supernatant gradually increased, again verifying the dissociation of the Pyridine-Pd\textsuperscript{II} complex (Supplementary Figures S12 and S13B). All the above experimental results demonstrated that [Cat\textsubscript{Py}-Pd\textsuperscript{II}]-Zn\textsuperscript{II} capsules had a chemically defined mechanism for the acid and base responsiveness due to the dynamic nature of the reversible coordination of polyphenol and pyridine.
Figure 2. The formation and acid/base dual-responsive dissociation of \([\text{Cat}_{\text{Py}}\text{-Pd}^{\text{II}}]\)-\(\text{Zn}^{\text{II}}\) capsules. (A) TEM image of \(\text{Cat}_{\text{Py}}\text{-Pd}^{\text{II}}\) primary nanoparticles, SEM images of the \([\text{Cat}_{\text{Py}}\text{-Pd}^{\text{II}}]\)-\(\text{Zn}^{\text{II}}\)-coated \(\text{CaCO}_3\), and bright-field microscopy image after \(\text{CaCO}_3\) removal. The inset picture showed the \([\text{Cat}_{\text{Py}}\text{-Pd}^{\text{II}}]\)-\(\text{Zn}^{\text{II}}\) complex particles on the surface of \(\text{CaCO}_3\). (B) EDX elemental mapping (Pd and Zn) of the \([\text{Cat}_{\text{Py}}\text{-Pd}^{\text{II}}]\)-\(\text{Zn}^{\text{II}}\)-coated \(\text{CaCO}_3\). (C) Bright-field microscopy images of \([\text{Cat}_{\text{Py}}\text{-Pd}^{\text{II}}]\)-\(\text{Zn}^{\text{II}}\) capsules incubated 5 h at pH 3.0, pH 7.0, and pH 10.0 solutions, respectively. (D) Heat map showing the percentage of remaining rate of capsules at different pH values; 100 capsules of each sample were measured. (E) Coordination dissociation images of Pyridine-Pd\(^{\text{II}}\) under basic conditions. (F) Characterization of reversible pH-dependent complexation between pyridine and Pd\(^{\text{II}}\) ions by HPLC spectrum. (G) pH dual-responsive mechanism of \([\text{Cat}_{\text{Py}}\text{-Pd}^{\text{II}}]\)-\(\text{Zn}^{\text{II}}\) capsules.

**UV/Vis dual-responsive controlled permeability of \([\text{Cat}_{\text{Azo-PCD}}\text{-PCD}]\)-\(\text{Fe}^{\text{III}}\) capsules**

Stimuli-responsive capsules to controllably release cargo by utilizing external triggers are important in various fields including drug delivery and sensing.\(^{35}\) Light is highly...
efficient, noninvasive, and environmentally friendly as an external stimuli method. Stimuli-responsive mechanisms of “smart” capsules may be further extended when light triggering is combined with MPN systems, especially utilizing light stimuli to selectively control encapsulation and release of cargo. Since the first discovery of the cis-form azobenzene under ultraviolet (UV) light, azobenzene has become one of the most widely investigated light-responsive molecular photoswitches between trans and cis isomers.\textsuperscript{36-40} Cyclodextrin (CD) with a cyclic structure is strongly polarized on the outside of the cavity due to the action of the hydroxyl group, while the inside side is nonpolar, which makes the cyclodextrin molecule suitable as a supramolecular host to coat guest azobenzene molecules.\textsuperscript{18,41} The incorporation of azobenzene group and PCD polymer into MPNs was a key way to implant smart on-off photoswitches into the network structures, conferring the MPNs with convertible properties in response to external stimuli. Cat\textsubscript{Azo}-PCD primary nanoparticles combined the light-responsiveness of Cat\textsubscript{Azo} with the host-guest interaction of PCD, resulting in UV/Vis dual-responsive controlled permeability of [Cat\textsubscript{Azo}-PCD]-Fe\textsuperscript{III} capsules (Figure 3A). TEM image revealed that the size of the Cat\textsubscript{Azo}-PCD particles was about 100 nm, which was consistent with the results obtained by DLS analysis (Figure 3B). [Cat\textsubscript{Azo}-PCD]-Fe\textsuperscript{III} capsules were deposited on sacrificial CaCO\textsubscript{3} templates and formed replica particles or capsules following template removal (Figure 3B, Supplementary Section S1.7). SEM images exhibited a rough surface confirming the presence of the [Cat\textsubscript{Azo}-PCD]-Fe\textsuperscript{III} coatings on the CaCO\textsubscript{3} template (SEM, Figure 3B). The monodisperse, spherical [Cat\textsubscript{Azo}-PCD]-Fe\textsuperscript{III} capsules observed from bright-field microscopy images highlights the stability of the free-standing networks after template removal (Figure 3A). Furthermore, EDX elemental mapping revealed that C, N, O, and Fe were all uniformly distributed throughout the [Cat\textsubscript{Azo}-PCD]-Fe\textsuperscript{III}-coated CaCO\textsubscript{3}, indicating that the [Cat\textsubscript{Azo}-PCD]-Fe\textsuperscript{III} is composed of Cat\textsubscript{Azo}-PCD nanoparticles and Fe\textsuperscript{III} ions (Supplementary Figure S14).

To assess the controllable permeability with UV/Vis dual-responsive controlled permeability of the [Cat\textsubscript{Azo}-PCD]-Fe\textsuperscript{III} capsules, the samples were incubated with an equal volume of fluorescein isothiocyanate-labeled dextran molecule solution (FITC-dextran, 1 mg ml\textsuperscript{-1}, 500 kDa). Under UV/Vis light irradiation, as shown in Figure 3C, [Cat\textsubscript{Azo}-PCD]-Fe\textsuperscript{III} capsules showed different permeability (Supplementary Figure S15). Specifically, the capsules (70.5\%) under UV light irradiation (632 mW cm\textsuperscript{-2}) showed higher permeability to 500 kDa FITC-dextran than the capsules (37.5\%) under visible light irradiation (3.0 mW cm\textsuperscript{-2}) (Figure 3G). These results are attributed to the strong binding affinity of trans-Azo to β-CD, while the weak binding affinity of cis-Azo to β-CD in the aqueous solution, so that the inclusion complexation between β-CD and Azo is reversible by Azo photo-isomerization.\textsuperscript{42,43} As validated in Figure 3A, the UV/Vis light-driven trans-to-cis and cis-to-trans conformational transformation of the Cat\textsubscript{Azo} molecule changed the host-guest interaction between the Cat\textsubscript{Azo} molecule and the PCD polymer, resulting in the looseness change of the [Cat\textsubscript{Azo}-PCD]-Fe\textsuperscript{III} capsules, which induced the reversible permeability of the [Cat\textsubscript{Azo}-PCD]-Fe\textsuperscript{III} capsules to FITC-dextran. The photoisomerization of Cat\textsubscript{Azo} was then investigated in UV/Vis spectroscopic studies by performing both the trans-to-cis isomerization and the cis-to-trans relaxation.
The original trans-Cat$_{Azo}$ showed a strong absorption maximum peak at 325 nm, arising from the π-π* azobenzene transition. Turning on the UV light at 632 mW cm$^{-2}$ and extending the irradiation time, a gradually decreased intensity of π-π* absorption band at 325 nm and an increased intensity corresponding to n-π* bands at 440 nm were observed. The maximum isomerization of Cat$_{Azo}$ is reached after around ~ 60 s (Figure 3D). These results indicated that the azobenzene moieties were photoisomerized from the trans- to the cis-form. The percentage of the cis-Cat$_{Azo}$ unit was about 73% (Supplementary Figure S16A and Section S1.10). Subsequently, exposure of the Cat$_{Azo}$ to a low-powered LED visible light (3.0 mW cm$^{-2}$) triggered the recovery of the absorption peak at 325 nm (Figure 3E), demonstrating a relaxation of cis- into a more stable trans-state (Supplementary Figure S16B and Section S1.10). Interestingly, this reversible photoisomerization process of the solution can be re-executed multiple times by alternative irradiation upon UV and Vis light (Figure 3F, absorbance at irradiation time $t$/initial absorbance, $A_t/A_0$, at 325 nm).

The [Cat$_{Azo}$-PCD]-Fe$_{III}$ capsules were investigated further to assess whether their permeability could be additionally tuned with changes in the alternative UV/Vis light. As observed from Figure 3G (left), the impermeability of the light-responsive capsules generally increased when the irradiation light was changed from UV light to visible light, conversely, the impermeability of the light-responsive capsules decreased. Specifically, 19%–22% of the capsules were impermeable to 500 kDa FITC-dextran under UV light. However, when the irradiation light changed from visible to UV light, the impermeability increased to 47%–65%. Repeated UV/Vis irradiation cycles induced the reversible trans-cis-trans changes in the [Cat$_{Azo}$-PCD]-Fe$_{III}$ capsules, further confirming the switchable “open-closed” state property of the capsules with light regulation (Figure 3G (right)). In addition to the UV/Vis dual-responsive permeability, the macroscopic surface properties (for example, wettability) of the surfaces could also be tuned using the light-driven host-guest interaction of [Cat$_{Azo}$-PCD]-Fe$_{III}$ (Figure 3H). [Cat$_{Azo}$-PCD]-Fe$_{III}$ coatings can make the surface of CaCO$_3$ hydrophilic (~14°) through the host-guest interaction between trans-Cat$_{Azo}$ and PCD driven by Vis light or hydrophobic (~115°) through the dissociation of cis-Cat$_{Azo}$ and PCD driven by UV light. Furthermore, the wettability can be easily altered by UV/Vis stimulation.
Figure 3. The formation and UV/Vis dual-responsive controlled permeability of [CatAz0-PCD]-FeIII capsules. (A) Schematic of the effect of UV/Vis light on [CatAz0-PCD]-FeIII capsules permeability to FITC-dextran (500 kDa). (B) TEM image of primary nanoparticles (CatAz0-PCD), SEM images of the [CatAz0-PCD]-FeIII-coated CaCO3, and bright-field microscopy image after CaCO3 removal. The inset picture showed the [CatAz0-PCD]-FeIII complex particles on the surface of CaCO3. (C) Confocal fluorescence microscopy images of [CatAz0-PCD]-FeIII capsules incubated with FITC-dextran (500 kDa) under UV/Vis light irradiation (the capsule permeability can be inferred by the contrast in fluorescence between the inner and outer environment). (D) UV-Visible absorption spectra of trans-to-cis isomerization for CatAz0 in THF under UV light (632 mW cm⁻²) and (E) cis-to-trans reversible isomerization for CatAz0 in THF under visible light (3.0 mW cm⁻²), inset: The enlarged view of the absorption peak in the visible region. (F) Reversible absorbance variation (325 nm) of CatAz0 in THF under periodic UV/Vis light irradiation. (G) Impermeability
of the [CatAzo-PCD]-Fe\textsuperscript{III} capsules under periodic UV/Vis light irradiation. (H) Tunable surface wettability through periodic UV/Vis light irradiation.

**Rapid fluorescence labeling of living cells by [CatOle-X]-Fe\textsuperscript{III}**

Cell tracking with fluorescence is significant to efficiently understanding cell migrations for cell-based therapies\textsuperscript{44−46} However, existing methods are often limited and slow in many cases. In particular, widely used fluorescent dyes (e.g., 3,3'-dioctadecyloxacarbocyanine perchlorate (DiO), 1,1'-dioctadecyl-3,3',3'-tetramethylindodicarbocyanine,4-chlorobenzenesulfonate salt (DiD), and 1,1'-dioctadecyl-3,3',3'-tetramethylindocarbocyanine perchlorate (DiI)) were often restricted due to the requirement on appropriate incubation time (10 ~ 20 min), quick fluorescence quenching, and insufficient stability in light and biological environments\textsuperscript{47,48} Fluorescent nanoparticles, with their small size, high surface area, and high surface reactivity are promising materials for rapid cell tracking\textsuperscript{49,50} To this end, we explored a universal approach with the rationally designed fluorescent primary nanoparticles, which could be broadly applied for the instant labeling of cells with various dyes to facilitate cell tracking studies. Synthesized CatOle molecules with long-chain alkane structures can be assembled with any hydrophobic cargo molecule “X”, especially fluorescent dyes, including coumarin 6 (C6), cyanine3 carboxylic acid chloride (Cy3), 5-aminofluorescein (5-AFM), and cyanine5 carboxylic acid chloride (Cy5), through hydrophobic interactions to form CatOle-X primary nanoparticles, which are capable of overcoming the intrinsic limitations of conventional fluorescent dyes (**Supplementary Section S1.4**).\textsuperscript{51} Furthermore, these CatOle-X nanoparticles can rapidly assemble (~ 1 min) with Fe\textsuperscript{III} ions to coat the cell surface with rapid fluorescence labeling due to the high adherence of polyphenols (**Supplementary Section S1.7**).\textsuperscript{20,21,52} Figure 4A showed that the generalized fluorescent dyes toolbox of [CatOle-X]-Fe\textsuperscript{III}-coated cells can be applied to a variety of hydrophobic fluorescent dyes. Here, B16 cells as model cells integrated with a range of fluorescent dyes, including C6, Cy3, 5-AFM, and Cy5 (**Supplementary Section S1.5**). Figure 4B illustrated the uniform and thin fluorescent layer with different luminescent colors on the surfaces of cells, indicating the successful assembly of CatOle-X nanoparticles on cells and the creation of at least four different types of biohybrid systems with different fluorescent layers.

To validate the reliability of the [CatOle-X]-Fe\textsuperscript{III} labeling strategy for biomedical studies (specifically the use of [CatOle-X]-Fe\textsuperscript{III} for fluorescence labeling of living cells), we chose [CatOle-C6]-Fe\textsuperscript{III} for further exploration. TEM images showed that the morphology of the CatOle-C6 complex was spherical particles with a size of about 100 nm, which was consistent with the particle size measured by DLS (**Figure 4C, Supplementary Figure S6**). Rough particles were present on the cell surface by the SEM images confirming the presence of the [CatOle-C6]-Fe\textsuperscript{III} coatings on the cell surface (**Figure 4C**). Moreover, EDX elemental mapping revealed the elemental compositions of [CatOle-C6]-Fe\textsuperscript{III} coatings (**Supplementary Figure S17**). We next examined the cytotoxicity of the Fe\textsuperscript{III} ion solution, CatOle-C6 nanoparticles, and [CatOle-X]-Fe\textsuperscript{III} complex with B16 cells (**Supplementary Section S1.11**). The labeled particles showed negligible cytotoxicity to cells even after 60 min incubation (**Figure 4D**). To
investigate the rapid (~ 1 min) fluorescence labeling of the [CatOle-C6]-FeIII on cells, cells were first labeled with blue nuclei-specific Hoechst 33342 and then treated with DiO (a cell membrane dye), and [CatOle-C6]-FeIII complex for 1 min, respectively. As shown in Figure 4E, green signals represented cell membrane dyed by DiO and [CatOle-C6]-FeIII complex respectively. It can be found that a strong green fluorescence was observed in cells cultured with [CatOle-C6]-FeIII complex, while rather weak signals were detected for cells incubated with the DiO cell membrane dye (Figures 4E and 4F). Quantitative measurements from flow cytometry also verified the above result (Figures 4G and 4H). Subsequently, we examined the colocalization of [CatOle-C6]-FeIII complex via dually labeling cells with blue nuclei-specific Hoechst 33342 and red DiD cell membrane dye. As shown in Figure 4I, blue, red, and green signals represented nuclei, the cell membrane dyed by DiD, and [CatOle-C6]-FeIII complex, respectively. The fluorescence signal of the [CatOle-C6]-FeIII complex was well overlapped with that of DiD, indicating that [CatOle-C6]-FeIII complex was primarily distributed on the cell membrane (Figure 4I). Compared with DiD, the fluorescence intensity of [CatOle-C6]-FeIII complex was stronger, as well indicating the rapid (~ 1 min) fluorescence labeling of [CatOle-C6]-FeIII complex (Figure 4I). Moreover, the green fluorescence of the [CatOle-C6]-FeIII complex was stable throughout these steps, demonstrating the photostability of the coated cellular compartments. Importantly, the particles outside the cell did not interact with the nucleus (blue) and cell membrane (red or green) labeling reagents, suggesting that [CatOle-C6]-FeIII coatings were not compromised by external interfering fluorescent molecules (Figures 4E and 4I).
Figure 4. Versatile dyes toolbox of [CatOle-X]-Fe\textsuperscript{III}-coated cell and the conferred rapid fluorescence labeling capabilities. (A) Chemical structures of various
fluorescent dyes. (B) [CatOle-X]-Fe$^{III}$-coated cell allows the engineering of cell-based biohybrid systems from four types of dyes. Confocal fluorescence microscopy images of representative [CatOle-C6]-Fe$^{III}$-coated cell, [CatOle-Cy3]-Fe$^{III}$-coated cell, [CatOle-5-AFM]-Fe$^{III}$-coated cell, and [CatOle-Cy5]-Fe$^{III}$-coated cell. Scale bars are 20 µm. (C) TEM image of primary nanoparticles (CatOle-C6) and SEM images of the [CatOle-C6]-Fe$^{III}$-coated cell. The inset picture shows the [CatOle-C6]-Fe$^{III}$ complex particles on the surface of the cell. (D) The cell viability of cells was detected by CCK8 assay after incubation with Fe$^{III}$ ion solution (500 µg mL$^{-1}$), CatOle-C6, and [CatOle-C6]-Fe$^{III}$ for a different time. Data are presented as mean ± SD. (n = 3). (E) Confocal fluorescence microscopy images of DiO-labeled cell membrane and [CatOle-C6]-Fe$^{III}$-coated cell. The concentration of dyes (DiO and C6) was 5 µM. The nuclei (blue) were stained with Hoechst 33342. Scale bars are 20 µm. The fluorescence intensity analysis (F) was performed by Image J. (G) Flow cytometry detection of DiO labeling cell membrane and [CatOle-C6]-Fe$^{III}$-coated cell at the same dye concentration; the colored lines show the fluorescence intensity distributions. The same volume of cells was used as a control group. The mean fluorescence intensity analysis (H) was performed by Image J. Statistical significance was calculated via one-way ANOVA with Tukey’s multiple comparisons (*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001). (I) Detection of colocalization of [CatOle-C6]-Fe$^{III}$-coated DiD-labeled cells by confocal fluorescence microscopy images. The scale bar is 5 µm. The fluorescence intensity and colocalization analysis were performed by Image J.

**Conclusion**

In summary, we demonstrated a universal approach to preparing customizable metal-phenolic supraparticles based on rationally designed phenolic building blocks. Three modified phenolic molecules (CatPy, CatAzo, and CatOle) with different functional moieties were successfully synthesized by the amidation strategy. The designed phenolic building blocks enable a simple, rapid, and integrative self-assembly process with ligands (Pd$^{II}$ ions, PCD, and hydrophobic cargo molecule “X”) by coordination interaction, hydrophobic interaction, and host-guest interaction to obtain primary nanoparticles (CatPy-Pd$^{II}$, CatAzo-PCD, and CatOle-X). The introduction of primary nanoparticles with different functionalities endows metal-phenolic supraparticles with corresponding functional properties, such as acid/base dual-responsive dissociation properties, UV/Vis dual-responsive controlled permeability, and rapid fluorescence labeling, thus enabling the rational customization of metal-phenolic supraparticles. Our results not only present a novel and universal platform for systematically introducing self-assembly strategies into MPNs, but also contribute to a conceptual and practical paradigm for smart MPNs with structural complexity and functional diversity.

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J.G., Y.Z., J.W., and G.G. conceived the project. Y.Z. and J.W. conducted the experiments and performed data analyses. J.X. directed the cell experiments. X.L. assisted with the cell image experiments. Y.Z., G.G., J.S., Y.H., J.G., J.J.R., J.W., and J.P. drafted the manuscript. All the authors discussed the results and commented on the manuscript.

Competing interests
The authors declare no competing interests.

Data and materials availability
All data are available in the main text or the Supplementary Information.

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