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Biocatalysts

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Semiconducting Polymer Nanobiocatalysts for Photoactivation of Intracellular Redox Reactions

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Abstract: An organic semiconducting polymer nanobiocatalyst (SPNB) composed of a semiconducting polymer core conjugated with microsomal cytochrome P450 (CYP) has been developed for photoactivation of intracellular redox. The core serves as the light-harvesting unit to initiate photoinduced electron transfer (PET) and facilitate the regeneration of dihydronicotinamide adenine dinucleotide phosphate (NADPH), while CYP is the catalytic center for intracellular redox. Under light irradiation, the semiconducting core can efficiently catalyze the generation of NADPH with a turnover frequency (TOF) 75 times higher than the reported nanosystems, ensuring the supply of the cofactor for intracellular redox. SPNB-mediated intracellular redox thus can be efficiently activated by light in living cells to convert the model substrate and also to trigger the bioactivation of anticancer drug. This study provides an organic nanobiocatalytic system that allows light to remotely control intracellular redox in living systems.

Specific control of biochemical reactions in living systems is of great interest because it represents a promising strategy to decipher the related biological functions and can potentially lead to new therapeutic modalities. Although physical (light and thermal),^[1] chemical (small molecular inhibitors),^[2] and biological (second messengers)^[3] signals can be used to control biochemical reactions, light has the advantages of affordable cost, low toxicity, flexible tunability, and fine spatiotemporal resolution and is most desired for non-invasive remote regulation.^[4] Among different biochemical reactions, intracellular redox plays a pivotal role in transferring energy, biosynthesizing metabolites, bioactivating drugs, and detoxifying xenobiotics within cells.^[5] Inspired by natural photosynthesis, optical agents including organic dyes, quantum dots, carbon nitrides, carbon dots, and peptide nanotubes have been used as artificial photocatalysts to activate redox via photoinduced electron transfer (PET) in solutions.^[6] However, the activation process of those nanomaterials usually requires cytotoxic transition-metal components to enhance charge separation^[7] or mediators to facilitate electron transfer.^[8] Particularly, organic dyes not only depend on these metallic components,^[9] but also have

relatively poor photostability (Supporting Information, Figure S1).^[10] Owing to these limitations, existing optical agents have not been demonstrated for photoactivation of intracellular redox.

Semiconducting polymer nanoparticles (SPNs) have emerged as versatile optical agents for biological applications ranging from molecular imaging^[11] to phototherapy.^[12] Owing to their good biocompatibility and high photothermal conversion efficacy, SPNs can serve as light-responsive modulators to regulate heat-related biological functions including activation of protein ion channels^[13] and gene transcriptions.^[14] Furthermore, SPNs have efficient light-harvesting properties and their band gaps can be fine-tuned by the precursor polymers, making them effective as the electron donors for PET.^[15] Recently, SPNs have also been used to capture sunlight to accelerate the electron-transport rates in photosystem, enhancing the photosynthesis of chloroplasts.^[16] These studies proved that SPNs could be promising for remote activation of intracellular reactions.

Herein we report the development of a completely organic semiconducting polymer nanobiocatalyst (SPNB) and demonstrate its application for in situ photoactivation of intracellular redox in living cells. SPNB is composed of a water-soluble SPN and microsomal cytochrome P450 (CYP), which serve as the light-harvesting PET initiator and the catalytic center, respectively. Microsomal CYP, the most important P450-containing system in eukaryotic cells, is an endoplasmic reticulum attached protein cluster mainly containing CYP and cytochrome P450 reductase (CPR).^[17] Because CYPs conduct oxidation by indirect utilization of electrons transferred from the cofactor dihydronicotinamide adenine dinucleotide phosphate (NADPH) via CPRs, the intracellular redox reaction efficacy is significantly determined by the external availability of NADPH. Within SPNB, the SPN can harvest light and initiate PET to efficiently reduce nicotinamide adenine dinucleotide phosphate (NADP⁺) to NADPH, guaranteeing the adequate electron supply for CYP-catalyzed oxidation. Thus, SPNB enables in situ activation of intracellular redox under light irradiation.

To find the ideal PET initiator, four semiconducting polymers (SPs) including poly(9,9'-dioctylfluorenyl-2,7-diyl) (PFO), poly[(9,9'-dioctylfluorenyl-2,7-diyl)-*alt*-(benzo[2,1,3]thiadiazol-4,7-diyl)] (PFBT), poly[2,7-(9,9'-dioctylfluorene)-*alt*-4,7-bis(thiophen-2-yl)benzo-2,1,3-thiadiazole] (PFODBT) and poly[2,6-(4,4-bis(2-ethylhexyl)-4H-cyclopenta[2,1-*b*;3,4-*b'*]-dithiophene)-*alt*-4,7(2,1,3-benzothiadiazole)] (PCPDTBT) (Figure 1b) were used to prepare SPNs through nano-precipitation in the presence of an amphiphilic copolymer, polystyrene-*block*-poly(acrylic acid) (PS-*b*-PAA). The resulted SPNs had the carboxyl groups on the surface

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Figure 1. Synthesis and characterization of light-harvesting SPNs.

a) Illustration of the preparation of SPNs through nano-precipitation. b) Chemical structures of PFO, PFBT, PFODBT, and PCPDTBT used for the preparation of SPNs. c) DLS profiles, d) photographs, and e) optical absorption spectra of SPNs dispersed in PBS buffer (pH 7.4). Inset in (c): representative TEM image of SPN-PFBT. [SPN] = 15 $\mu\text{g mL}^{-1}$ in photographs.

(Figure 1a), endowing them with not only the water stability but also the ability for post-conjugation. Dynamic light scattering (DLS) showed the similar sizes of these carboxyl SPNs (21–26 nm) (Figure 1c; Supporting Information, Figure S2), while transmission electron microscopy (TEM) illustrated their spherical morphologies (Figure 1c, inset; Supporting Information, Figure S3). The SPNs solutions remained stable and transparent in buffer with no size change after stored at room temperature for 8 weeks (Figure 1d; Supporting Information, Figure S4). Dependent on their band gaps, the absorption maxima of SPNs were located at 381 (SPN-PFO), 460 (SPN-PFBT), 536 (SPN-PFODBT) and 660 nm (SPN-PCPDTBT) (Figure 1e); while their emission maxima were at 436 (SPN-PFO), 542 (SPN-PFBT), 691 (SPN-PFODBT), and 816 nm (SPN-PCPDTBT; Supporting Information, Figure S5). In particular, their broad absorption bands made them efficient in harvesting visible light.

As the most common natural redox equivalents, NAD(P)H transfers electrons for over 80% oxidoreductases in biological systems and is closely associated with their catalytic efficacies. The energy levels of the SPNs were thus examined to check if they could fulfill the thermodynamic requirement for the photocatalyzed reduction of NADP^+ to NADPH. The reduction potentials of SPNs were measured by cyclic voltammetry, showing -1.89 , -1.56 , -1.46 , and -1.41 V for SPN-PFO, SPN-PFBT, SPN-PFODBT, and SPN-PCPDTBT, respectively (Figure 2a; Supporting Information, Figure S6). These values were similar to those of corresponding SPs calculated from the reported lowest unoccupied molecular orbital (LUMO) energy levels (PFO: -1.9 , PFBT: -1.5 ,

Figure 2. Light-driven generation of NADPH catalyzed by SPNs.

a) Energy level diagram of SPNs and a representation of photocatalysis mechanism for the reduction of NADP^+ to NADPH. b) Representative photocurrent responses of SPN-PFBT and SPN-PFODBT on an ITO electrode with the interval of 20 s, which were recorded at 0 V bias in phosphate buffer (100 mM, pH 6.0) containing 15% triethanolamine (TEOA) as electron donors. c) The temporal performances and d) turn-over frequencies (TOFs) of SPNs for photocatalysis of NADPH generation.

PFODBT: -1.3 , and PCPDTBT: -1.3). Thereby, the formation of nanoparticles had minimal effect on reduction potentials. More importantly, the reduction potentials of these SPNs were all higher than that of a $\text{NADP}^+/\text{NADPH}$ couple (-0.87 V vs. Ag/AgCl) (Figure 2a), ensuring the efficient PET from SPNs to NADP^+ to generate NADPH.

Because the efficiency of photoinduced charge separation is important to the catalytic ability of a photocatalyst, the time-resolved responses of photocurrent to periodical illumination were studied for the SPNs. To avoid the potential toxicity caused by UV light, light illumination was conducted under visible light (Xe lamp, >420 nm). Upon light irradiation, both SPN-PFBT and SPN-PFODBT generated typical anodic photocurrents with a sharp spike (Figure 2b). Moreover, the current density generated by SPN-PFBT was 4.8-fold higher than that by SPN-PFODBT at the plateau, suggesting the stronger charge separation efficacy for SPN-PFBT. By contrast, the photocurrents generated by SPN-PFO and SPN-PCPDTBT showed a mixed type of kinetic traces (Supporting Information, Figure S7): a sharp spike of anodic photocurrents immediately appeared upon light irradiation, and then an inversion of photocurrents was developed, ending up with a cathodic spike after light irradiation. The transient anodic photocurrent suggested the presence of surface states different from the bulk for SPN-PFO and SPN-PCPDTBT, which was less relevant to the photocatalytic efficacy of dispersed SPNs in solutions. As confirmed by the current densities, the order of photoinduced charge separation efficacy was: SPN-PFBT $>$ SPN-PFODBT $>$ SPN-PCPDTBT $>$ SPN-PFO, which is partially consistent with their reduction potentials except for SPN-PFO. Owing to the absence of donor–acceptor structure in PFO and weak

visible-light absorption, SPN-PFO with the highest reduction potential however showed the lowest charge separation efficacy among four SPNs.

The photocatalytic abilities of these SPNs were then studied and compared in terms of reducing NADP^+ to NADPH. The generation of NADPH was monitored by measuring the absorption at 340 nm every 12 min during light irradiation. At each timepoint, the amounts of generated NADPH followed the order: SPN-PFBT > SPN-PFODBT > SPN-PCPDTBT > SPN-PFO (Figure 2c). After 1 h light irradiation, the generated NADPH catalyzed by SPN-PFBT was 1.3-, 1.9-, and 2.8-fold higher than that by SPN-PFODBT, SPN-PCPDTBT, and SPN-PFO, respectively. The turnover frequencies (TOFs) were estimated to be 133.6 h^{-1} , 105.3 h^{-1} , 68.8 h^{-1} , and 48.6 h^{-1} for SPN-PFBT, SPN-PFODBT, SPN-PCPDTBT, and SPN-PFO (Figure 2d), respectively. As compared with the reported nanomaterials such as peptide nanotubes ($\leq 1.78 \text{ h}^{-1}$), these SPNs not only had much higher TOFs,^[7b] but also exhibited comparable or even better kinetic performance to catalyze NAD(P)H generation despite being without Pt or TiO_2 , mediator ($[\text{Cp}^*\text{Rh}(\text{bpy})\text{H}_2\text{O}]^{2+}$), and enzyme usage (Supporting Information, Figure S8). The order of photocatalytic abilities of these SPNs to generate NADPH was consistent with that of their charge separation efficacies. Note that among these four SPNs, SPN-PFBT was the best photocatalyst, mainly because of its highest charge separation efficacy and the relatively more negative reduction potential.

Next, SPN-PFBT and SPN-PFODBT were chosen to activate microsomal CYP-catalyzed redox towards the substrate, 7-benzoyloxy-4-trifluoromethyl coumarin (BFC), in solutions. The reaction efficacy was monitored by the fluorescence increase as the oxidation of non-fluorescent BFC produced the fluorescent product, 7-hydroxyl-4-trifluoromethyl coumarin (HFC). After 1 h light irradiation, the fluorescence increment for the SPN-PFBT activated CYP system was 1.46-fold higher than that for SPN-PFODBT (Figure 3a), while BFC or BFC with microsomal CYP alone barely showed fluorescence increase. Moreover, the fluores-

cence increases in the presence of SPNs alone were 3 to 4.3 times lower than their corresponding enzymatic systems, proving that the generation of HFC was mainly attributed to the redox catalyzed by SPN-activated microsomal CYP. Moreover, in terms of CYP, the enzymatic catalytic efficiencies (k_{cat}/K_m) were improved by 283- and 33-fold for SPN-PFBT ($0.26 \mu\text{M}^{-1} \text{min}^{-1}$) and SPN-PFODBT ($0.03 \mu\text{M}^{-1} \text{min}^{-1}$) respectively, compared with that of the wild-type (WT; $0.00092 \mu\text{M}^{-1} \text{min}^{-1}$) (Figure 3b; Supporting Information, Figure S9 and Table S2).

The SPN-PFBT-mediated photoactivation of microsomal CYP-catalyzed redox was tested against nifedipine, a drug used to block calcium channels to treat high blood pressure and primarily metabolized by microsomal CYP to the deactivated form (dehydronifedipine). After light irradiation for 20 min in the presence of microsomal CYP and SPN-PFBT, most nifedipine (HPLC retention time, $T_R = 19.3 \text{ min}$) was oxidized to dehydronifedipine ($T_R = 15.7 \text{ min}$; Figure 3c), as confirmed by electrospray ionization-mass spectrometry (ESI-MS) analysis (Supporting Information, Figure S10). In contrast, dehydronifedipine was marginally generated if one component of SPN, enzyme and light was absent. Note that the peak at $T_R = 18.8 \text{ min}$ was attributed to the light-induced degradation because of the light sensitivity of nifedipine. Thus, SPN-PFBT was able to activate microsomal CYP-catalyzed redox against both model and clinically-relevant substrates.

Because of the good cytocompatibility of SPNs (Supporting Information, Figure S11), SPN-PFODBT was used for intracellular regulation. SPNB was synthesized by conjugating to microsomal CYPs via a carbodiimide coupling reaction between carboxyl groups of the nanoparticles and amine groups of the enzymes. The increased diameter measured by DLS and slower migration rate of electrophoresis confirmed the successful bioconjugation (Figure 4b; Supporting Information, Figure S12). The resulting nanoparticles were delivered into the living liver hepatocellular cells (HepG2) and the in situ photoactivation of SPNB-catalyzed intracellular redox was assessed using BFC as the substrate. The minimal overlap for the emission spectra of the generated HFC and SPN-PFODBT ensured the fluorescence tracking of both components.

After being cultured with SPNB overnight, HepG2 cells were incubated with BFC for 2 h and then exposed to light irradiation with the supply of NADP^+ for 30 min before fluorescence cell imaging. The SPNBs and the product (HFC) were indicated as pseudo red and green, respectively. Upon irradiation, the green fluorescence in SPNB-treated cells significantly increased by 1.7-fold compared with that without irradiation, and was 42.5-fold higher than that in the control cells without SPNB-treatment regardless of irradiation (Figures 4c,d; Supporting Information, Figure S13). Note that SPNB-treated cells had higher green fluorescence than the control cells without light irradiation. This was caused by the increased amount of microsomal CYP in living cells contributed by SPNB that enhanced the intrinsic oxidation of BFC in living cells. These data confirmed that the SPNB-catalyzed intracellular redox could be activated following the proposed mechanism in Figure 4a: upon light irradiation, the

Figure 3. SPN-mediated photoactivation of microsomal CYP-catalyzed redox in solutions. a) The fluorescence increases at 500 nm caused by the oxidation of substrate BFC as a function of light irradiation time under the following conditions: BFC alone, BFC with microsomal CYP, BFC with SPN-PFODBT or SPN-PFBT, BFC with both microsomal CYP and SPN-PFODBT or SPN-PFBT. b) Kinetic studies of CYP-catalyzed oxidation activated by SPN-PFBT or SPN-PFODBT, compared with that of the wild-type (WT). c) Chromatograms of SPN-mediated photoactivation of microsomal CYP-catalyzed redox against nifedipine under various conditions indicated. PFBT: SPN-PFBT; CYP: microsomal CYP; hv: light. The structures and peak positions of nifedipine (gray) and the metabolized product, dehydronifedipine (red), are indicated.

Figure 4. Photoactivation of SPNB-mediated intracellular redox in living cells. a) Illustration of the mechanism for photoactivation of SPNB-mediated intracellular redox. b) Agarose gel electrophoresis of SPNBs and the precursor SPN-PFODBT. c) Fluorescence images of SPNB-treated cells with or without light irradiation. d) The intensity quantification of green fluorescence from the oxidation of non-fluorescent BFC to fluorescent HFC in control cells and SPNB-treated cells with or without light irradiation. e) The mechanism of SPNB-mediated photoactivation of drug toxicity. f) The viabilities of drug-treated cells in the absence and presence of SPNB, with or without light irradiation. * No statistically significant difference in control cells with or without light irradiation ($p > 0.5$). ** Statistically significant difference in SPNB-treated cells with or without light irradiation ($p < 0.05$).

light-harvesting SPN core initiated the PET process, leading to the reduction of NADP^+ to NADPH; the electrons stored in NADPH were then used by CPRs and transported to the heme-iron center of CYPs, promoting the oxidation of non-fluorescent BFC to fluorescent HFC.

The proof-of-concept application of SPNB for drug activation was conducted using menadione (an anticancer drug) as the model drug. The oxidation of menadione into the active form (semiquinone radicals) was triggered by SPNB-catalyzed intracellular redox under light irradiation, leading to the generation of cytotoxic superoxide anions ($\text{O}_2^{\cdot-}$; Figure 4e). With irradiation, the viability of SPNB-treated cells decreased to 34 %, 2.7-fold lower than that without irradiation (90 %; Figure 4f). In contrast, cells only treated with drugs showed almost no toxicity regardless of irradiation, whose viabilities were slightly higher than that of SPNB-treated group without light irradiation.

In conclusion, we have synthesized an organic nanobiocatalyst (SPNB) composed of a light-harvesting SPN to initiate PET and a microsomal CYP to catalyze intracellular redox. Structural screening identified the optimal SPNs, showing the turnover frequency (TOF) of generating NADPH that is 75-times higher than the reported nanosystems. Such an efficient generation of NADPH ensured the adequate electron supply for CYP to perform the intracellular redox against both model substrate and clinical drugs. Coupled with the high cytocompatibility, SPNB can undergo

the light-triggered intracellular redox in living cells, yielding the reaction efficacy 42.5-fold higher than the intrinsic cellular reaction and increase the cytotoxicity by 2.7-fold for the tested drug. To the best of our knowledge, this study reports the first completely organic nanosystem that allows in situ regulation of intracellular redox. This work is also different from our previous work that utilizes the photo-thermal heat to control the biological systems.^[12a,13,14] In view of the high efficiency, such a nanobiocatalyst is promising to cooperate with other oxidoreductases to activate prodrug in vivo.

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Conflict of interest

The authors declare no conflict of interest.

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Communications

Biocatalysts

Y. Lyu, J. Tian, J. Li, P. Chen,
K. Pu*

Semiconducting Polymer
Nanobiocatalysts for Photoactivation of
Intracellular Redox Reactions

An organic nanobiocatalyst composed of a semiconducting polymer core conjugated with microsome cytochrome P450 (CYP) has been developed. It can

undergo an intracellular redox reaction that is non-invasively triggered by light in living cells.

Biokatalysatoren

Y. Lyu, J. Tian, J. Li, P. Chen,
K. Pu*

Semiconducting Polymer
Nanobiocatalysts for Photoactivation of
Intracellular Redox Reactions

Ein organischer Nanobiokatalysator besteht aus einem halbleitenden Polymerkern, der mit mikrosomalem Cytochrom P450 (CYP) konjugiert ist. Er kann

eine intrazelluläre Redoxreaktion eingehen, die in Lebzellen auf nicht-invasive Weise durch Licht ausgelöst wird.

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