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ARTICLE

Reduction-responsive Polypeptide Nanogel Encapsulating NIR Photosensitizer for Imaging Guided Photodynamic Therapy

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A new bromine substitution near infrared (NIR) cyanine Br_2-IR808 has been synthesized, and the heavy atom effect makes it an efficient photosensitizer with NIR fluorescence properties, and it can be used as both photosensitizer and fluorescence dye synchronously. An intelligent reduction-sensitive polypeptide nanogel has also been synthesized, and it worked as the nano-carrier for the Br_2-IR808 dye. The as-prepared NIR nanogel showed an imaging guided PDT properties for the *in vitro* studies, and the reduction-induced disassembly of the nanogel could promote both the delivery hydrophobic cyanine dye inside cell, and it also enhances the efficiency of the photosensitizer release, which makes the nanogel potential application as a NIR theranosis of cancer. In addition, only 2 μM photosensitizer Br_2-IR808 is required for the efficient PDT here while 30 μM IR808 is required solely as reported.

Introduction

Photodynamic therapy (PDT) has become an increasing attractive topic since Niels Finsen used red-light exposure to treat diseases at the end of the nineteenth century.[1,2] PDT acts in an oxygen-consuming way in the presence of light and photosensitizer, when the photosensitizer is exposed to light of a specific wavelength, it will transfer the energy of light to oxygen to generate the reactive oxygen species (ROS) which do extremely harm to tumours. Many efficient photosensitizer have been reported, such as Chlorin e6, BODIPY, (2-[1-hexyloxyethyl]-2-devinylpyropheophorbide-a (HPPH)), etc.[3] However, most photosensitizers are excited by visible or even UV light, which has limited penetration depth due to the light scattering and absorption by biological tissues, resulting in ineffective therapeutic effects to tumours.[4] The near infrared (NIR) window in the range of 690 - 1000nm is known as the optical tissue penetration window, in which biological tissues have the weak light absorption, ideal for optical imaging and phototherapy.[5-7] By now, the number of NIR photosensitizer is still scarce and new kinds of them should be developed.[8]

Imaging guided PDT has attracted much attention recently due to it provides a possibility to trace the movement of photosensitizer inside cells or body as well as monitoring the size change of the tumour during the therapy processes.[8-14] However, the utilization of NIR dyes as both the imaging agent and photosensitizers is still a challenge, especially combination with stimuli-responsive polymeric nano-carriers.[10]

Cyanines dyes have been widely used for imaging by virtue of their excellent optical properties in the NIR region, besides, some of them have been reported having photosensitizing characteristics.[15] Thus, a high singlet oxygen quantum yield is one of the most important qualities for an admirable photosensitizer which can be realized by utilizing heavy atom effects. Considering this, a novel cyanine dye Br_2-IR808 from IR808 has been developed here, aiming to achieve simultaneous real-time monitoring and tumour treating. In addition, the application of cyanine dyes meets its bottleneck *in vivo* therapy due to their tendency to aggregate in aqueous medium and limited selectivity to cancer cells. To solve this problem, researchers have developed various kinds of nanomaterials used as non-invasive carriers (e.g. liposomes and synthetic peptide-based polymers), among them peptides get much attention for their high biocompatibility and biodegradability.[16] Polypeptides synthesized from N-Carboxyanhydrides (NCA) monomers are of special interesting for their excellent properties as the nano-carriers for drug/gene delivery.

Intelligent polypeptides nano-carriers have attracted much attention recently. According to our group's previous work,[17] a kind of reduction-responsive nanogel containing disulfide bonds has been developed which can be degraded reductively since intracellular glutathione (GSH) content is higher than the extracellular and normal-cellular one.[13] Thus, a nanogel (mPEG-LLys-LCys) is synthesized through ring-opening polymerization of a-Amino Acid N-Carboxyanhydrides (NCA), in which mPEG is capable of improving the solubility of this system. In our prediction, it can encapsulate cyanine efficiently in its hydrophobic cores via hydrophobic interactions and will accumulate in tumour cells through enhanced permeability

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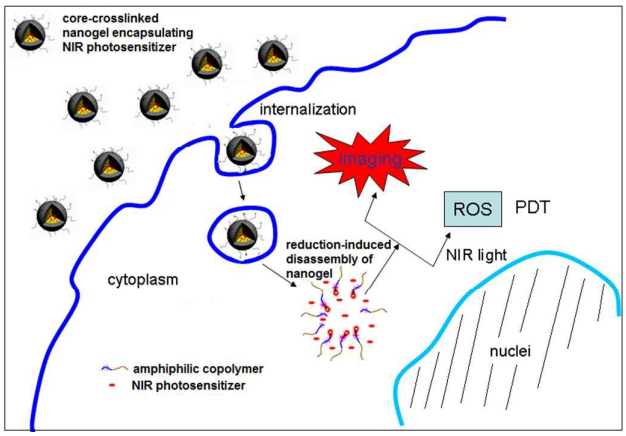
and retention (EPR) effect. On the other hand, the nanogel will degrade to release cyanine dyes when it reaches cells, and PDT and imaging will be effective when we put light into use. The MTT experiments upon HepG2 cells showed an obvious growth inhibition which means our presupposition proved to be true.

Here, a cyanine-loaded nanogel has been developed which was used as the nano-carrier for hydrophobic dye of Br_2-IR808, and imaging and PDT of HepG2 cells has been studied (Scheme 1).



Scheme 1. Internalization of the core-crosslinked nanogel containing NIR photosensitizer followed by reduction-induced NIR dye release for both imaging and PDT.

Results and discussion

Chemical synthesis and structure characterization

The cyanine dye IR808 was synthesized for improving the ability of singlet oxygen generation. Photosensitizer singlet-oxygen generation level was modulated by the exploitation of the heavy-atom effect,[18] and bromine atom substituent was introduced to the phenyl group of IR808. Figure 1 shows the synthesis route of Br_2-IR808, and the ammonium salt 3 was the key intermediate. Finally, cyanine 5 was obtained and confirmed by ^{1}H-NMR measurement and Mass Spectrometry (Fig.2).

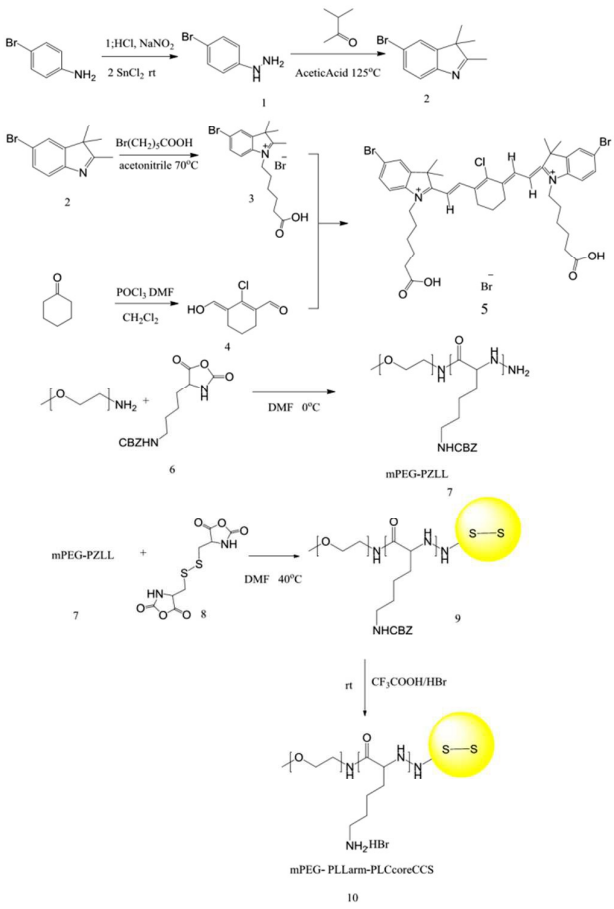


Figure 1: Synthesis route of cyanine dye of Br_2-IR808, and the disulfide bond crosslinked polypeptide nanogel

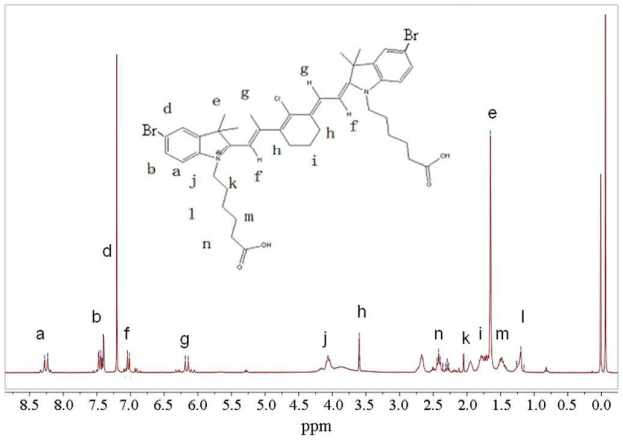


Figure 2. The ^{1}H-NMR spectrum of Br_2-IR808 NIR photosensitizer

Quantum yields of photosensitizer for singlet oxygen generation ($\phi_\Delta(^1O_2)$) were determined by monitoring the dye-sensitized photooxidation of 1,3-diphenylisobenzofuran (DPBF), and it was calculated using the standard, methylene blue (MB), by plotting the ΔOD of DPBF against the irradiation time.[19] As shown in Fig.3, the calculated $\phi_\Delta(^1O_2)$ is 0.046 for

Br_2-IR808 while it is 0.036 for IR808, indicating the adding of Br atoms enhances the quantum yields of photosensitizer for singlet oxygen generation.

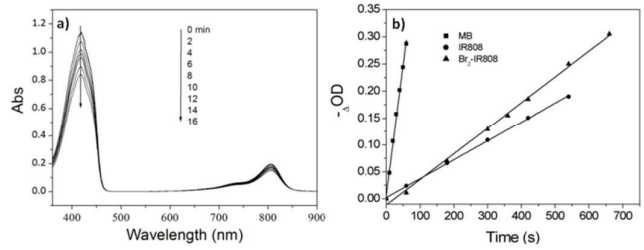


Figure 3. a) Absorption spectra of DPBF upon irradiation in the presence of Br_2-IR808 for different time; b)Plot of change in absorbance of DPBF at 418 nm at different irradiation time (λ_{irr}=808 nm) in the presence of Br_2-IR808 and IR808 using methylene blue as the standard in DMSO.

High molecular weight polypeptides could be prepared by ring-opening polymerization of NCA. The method is efficient and economical, and it has been applied to manufacturing fascinating structure like block, branch, or star copolymers.[17] Using arm-first strategy, biodegradable nanogels were prepared by a one-step process.[16] Generally, the preparation of a core cross-linked nanogel involves the synthesis of a macroinitiator, followed by the polymerization of a bifunctional or a multifunctional monomer in the presence of the macroinitiator.[20] Reduction-sensitive polymer is typically intelligent one which is widely being used as delivery systems in biomaterials,[21, 22] and these polymers usually contain disulfide linkages which is sensitive to glutathione (GSH) in the cell.[23] Recently, we reported the synthesis of a novel disulfide core cross-linked polypeptide nanogel with PEG arms by a one-pot ROP of L-Cystine N-carboxyanhydride (Cys-NCA) and γ-benzyl-glutamate N-carboxy-anhydride (BLG-NCA) by an amino group terminated macroinitiator $mPEG_{1900}$-NH_2, which showed good reduction-responsive DOX drug release behavior.[24]

Here, a two-step process was developed to prepare a core-corsslinked nanogel. At first, Lys NCA was polymerized using a primary amine macroinitiator, mPEG-NH_2, to afford arm, and then Cys-NCA monomer with disulfide bond linking was added, and the continuous ROP of the Cys-NCA result in the formation of a core-crosslinked nanogel with PEG-PZLL as it arms. The diblock polymer of PEG-PZLL was confirmed by GPC and NMR (Fig.S2). As shown in Fig.4a, the peak of retention time of macroinitiator mPEG-NH_2 is 10.2 min while it is 9.2 min for PEG-PZLL, indicating that the diblock polymer PEG-PZLL was obtained successfully. Moreover the diblock polymer is in a narrow molecular-weight distribution with PDI=1.14. NMR studies showed that the degree of polymerization is 12 of PZLL, which is consistence with the result of GPC measurement. The resonances of the methylene protons of the Cbz protecting group (δH, 4.9 ppm) were used as a reference for the calculation of the monomer.

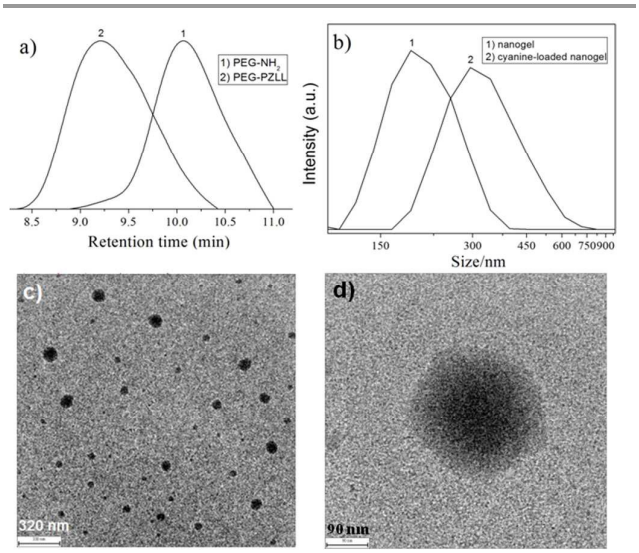


Figure 4. a) GPC of mPEG-NH_2 and diblock polymer PEG-PZLL; b) DLS of nanogel and cyanine-loaded nanogel; c)TEM micrographs of nanogel.

PEG-PZLL was then crosslinked by Cys-NCA monomer, which is hydrophobic and make the nanaogel reduction-sensitive.[25] The crosslinking-reaction was performed in 40℃ for 3 days and then the Cbz protecting group was de-protected by HBr treatment.[26] The S ratio of nanogel is 5.16% which indicated 70% of Cys-NCA monomers were consumed according to elemental analyses. The size and size distribution of the nanogels was studied by means of DLS and TEM.(Fig.4b and c) The mean diameter determined by DLS measurement is 238nm, while size given by TEM measurement is in range of 100-250nm. The shrinkage of TEM could be explained by the solvent evaporation during sample preparation as well as high arm ratio of nanogel. In addition, Figure 4d shows the TEM image of one nanogel, and clearly a core-shell structure can be found. Typically, the cyanine-loaded nanogel is larger than pure nanogel, indicating the encapsulating of cyanine dye results in the swelling of the nanogel.

The DLC and DLE of cyanine dye encapsulated by the nanogel were measured and they are 3.94% and 15.6% respectively, indicating the successful encapsulating of the photosensitizer by the nanogel. However, it is difficult to study the cumulative release of the photoseneitizer by means of traditional dialysis method for it forms precipitates inside the dialysis bag in PBS when the nanogel was disassembled by adding GSH. The reason is that the Br_2-IR808 is not dissolved in PBS. In order to make sure whether the encapsulated Br_2-IR808 can be released during the disassembly of the nanogel or not, mixture of PBS and ethanol was used as the media for the dye releasing study and dialysis, and Fig.1s shows the result of the releasing behaviour the nanogel to the solution outside the dialysis bag, and clearly Br_2-IR808 can be released from the nanogel in PBS and ethanol, and the adding of GSH could promote the release, indicating the efficient encapsulation by the nanogel. In order further to make sure the encapsulating ability and its reduction-sensitive release behaviour of the nanogel, typical hydrophobic drug DOX was

used as the model for the study. Diffusion and dialysis technique was applied to prepare DOX-loaded nanogel, and its reduction-sensitive release behaviour has been studied. As shown in Fig.5, under reduction-insensitive conditions, the cumulative amount of drug released from the dox-nanogel reaches 27% without GSH for 5 h, while in the presence of 10 mM GSH, a total release of the 50% drug after a period of 5 h can be found. At the end, 28% DOX released from DOX-loaded naonaogel under PBS without GSH. Meanwhile, DOX release in PBS with 10 mM GSH reaches 67%. It revealed that cleavage of the disulfide bond contributes to the fast DOX release from the nanogel in reductive conditions.

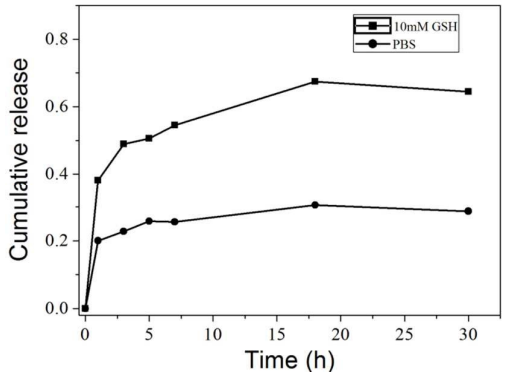


Figure 5. Cumulative release of DOX from DOX-loaded nanogel

Optical properties of cyanine and cyanine-loaded nanogel

Optical properties of cyanine as well as the cyanine-loaded nanogel were investigated. The absorption peak of cyanine located at 802nm for 10% FBS, 791nm for methanol and 919nm for PBS. The emission peak was 823nm for 10% FBS, and 818nm for methanol, respectively. All stokes shift is larger than 20nm. The red-shift in PBS may be due to H-aggregation of cyanine in aqueous solution. The quantum yield of the cyanine is 0.081 in methanol (ICG was used as a reference[17]), which is suitable for biomedical imaging.

Interesting, absorption properties cyanine-loaded nanogel is quite different with cyanine. Cyanine-loaded nanogel absorption peak were 748 and 807nm in PBS, and the absorption properties are similar to cyanine in PBS contained 1% butylamine. However, for a mixture of cyanine and mPEG-PZLL the Abs intensity in 807 nm of is much stronger than that of 748 nm, indicating that the primary amine of nanogel plays a key role for such difference (Fig.6c). The fluorescence recovery of cyanine-loaded nanogel in 10% FBS was shown in Fig.6. Both cyanine-loaded nanogel solution with and without GSH reached its maximum in 26h. A 4 folds fluorescence recovery can be found in 10% FBS with 10 mM GSH while it is only 1.39 folds was found in 10% FBS without GSH. As 10% FBS is good solvent for cyanine and there was no chemical bond between cyanine and nanogel, no surprise for fluorescence recovery without GSH. The fluorescence intensity of cyanine-loaded nanogel solution with GSH was 2.87 folds of solution without GSH. The strong fluorescence recovery could be considered that GSH broke of the disulfide bond of nanogel and then cyanine was released from the inner core of nanogel.[27]

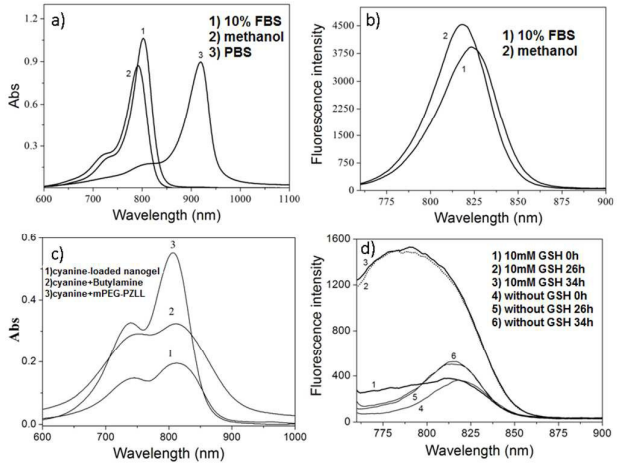


Figure 6. a)Absorption of cyanine in 10% FBS, methanol and PBS. All the concentration is 5 μg/ml; b) fluorescence of cyanine in 10% FBS, methanol. All the concentration is 5 μg/ml; c) absorption of cyanine-loaded nanogel (1.2 mg/ml) in PBS, cyanine (5 μg/ml) in PBS /Butylamine (volume ratio:100:1), and cyanine (5 μg/ml) mixed with mPEG-PZLL(45μg/ml) in PBS; d) The fluorescence recovery of cyanine-loaded nanogel in 10%FBS with or without GSH. (concentration: 0.125mg/ml)

***In vitro* cytotoxicity and imaging**

MTT assay was used to determine cellular phototoxicity. No obvious cytotoxicity was observed in this work even though the cyanine dye Br_2-IR808's concentrations reached 3.0 μM. However, the phototoxicity of cyanine is negligible in irradiated condition, and this may due to the low concentrations of Br_2-IR808 was internalized by cells during its high hydrophobicity.[15]

For cyanine-loaded nanogel we observed a significant decrease of cell viability in irradiated conditions compared to free cyanine in the same concentrations for Hepg2 cell. At 2μM, cytotoxicity of cyanine-loaded nanogel is negligible in non-irradiated condition while in irradiated condition it showed markedly cytotoxicity and the difference demonstrates the phototoxicity of cyanine-loaded nanogel. Cyanine-loaded nanogel was stimulated with NIR laser produced singlet oxygen, which is toxic to tumor cells.[13] When a higher concentration of 3μM, was used the cytotoxicity increased in non-irradiated conditions but phototoxicity did not have much improvement. A Simliar result has also been observed when MCF-7 cell was used (Fi7.b). To directly observe the phototoxicity, FDA/PI was applied to live/dead staining. The strong red fluorescence of PI can be observed under irradiated conditions, which are negligible in darkness. As shown in Fig.8, near all of the cells are alive in non-irradiated conditions while most of them dead when the NIR light irradiation were load and the cells inside the light cycle (indicated by yellow colour) dead efficiently when the cells outside the cycle are alive. For MTT experiment, the result is statistically, and the light spot is small, which results in the weak difference of cell viability between nor-irradiated or irradiated conditions, and the result in Fig.8 clearly revealed

the efficient PDT behaviour of the photosensitizer Br_2-IR808. It also reveals that the nanogel enhance the internalization of Br_2-IR808, furthermore enhance the phototoxicity.[28] Shi et al. utilized IR808 directly as the photosensitizer for PDF and it requires at least 30 μM IR808 to show markedly PDF result. However, here by using the polypeptide nanogel as the carrier only 2 μM of Br_2-IR808 is required for the similar PDT result, indicating the application of nanogel can efficiently reduce the amount of the photosensitizer, which makes it more safety.

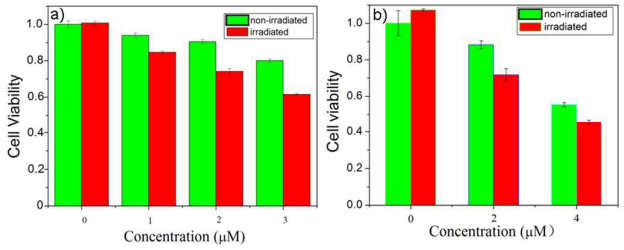


Figure 7. Cell viability of cyanine-loaded nanogel under dark or light for Hepg2 (a) and MCF-7 (b) cells.

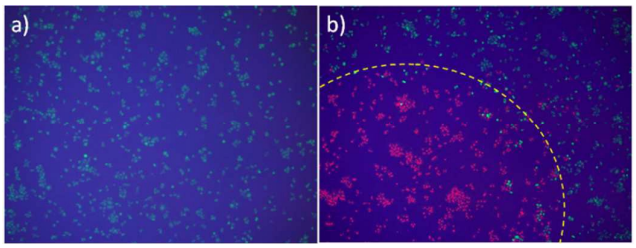


Figure 8: FDA/PI live/dead staining of cell incubated with cyanine-loaded nanogel PI:dead cells, red; FDA: live cells, green: a) non-irradiated condition, b) irradiated condition (magnification:×4).

Vitro imaging was shown in Fig.9. Fluorescence microscope was to determine optical properties in Hepg2 cells. After incubation with medium containing cyanine-loaded nanogel (1.0 μM) 6h in dark, fluorescence image was obtained by stimulated with red light. Figure 9 shows the images in both bright field and fluorescence. The strong fluorescence emission indicated the cyanine-loaded nanogel is suitable for biomedical imaging and good prospect in cancer diagnosis and treatment.

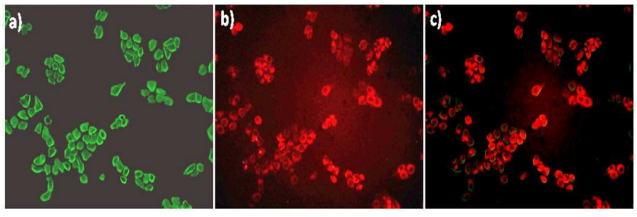


Figure 9. Cell imaging of cyanine-loaded nanogel. a) bright field, b) fluorescence image, and c) merged (magnification:×20).

Experimental

Materials

All agents were purchased from Aladdin Corporation (China) and without further purification while organic solvent were purchased from Sinoreagent Corporation. Dichloromethane (DCM), Hexane and THF were first refluxed with CaH_2 followed by distillation. DMF was stirred with CaH_2 at room temperature for 48h, and was then purified by vacuum distillation. Dialysis bags (cutoff M_w=8000/2000) were obtained from Bomei Biotechnology Corporation. Milli-Q Synthesis System (Millipore, Bedford, MA, USA) was applied to prepare Milli-Q water (18.2 MΩ).

Characterization.

^{1}H NMR spectra were measured on a Bruker AC 300 or 400 spectrometer. Deuterated dimethyl sulfoxide (DMSO) or deuterated chloroform containing 0.03 v/v % tetramethylsilane (TMS) was used as the solvent. Transmission electron microscopy measurement was performed on a on a JEOL-2010 microscope with an accelerating voltage of 200 KV. Size and size distribution of the nanogel were determined by dynamic light scattering (DLS) carried out on a Malvern Zetasizer Nano ZS90 with a He-Ne laser (633 nm) and 90 ^{o} collecting optics. Measurements were performed at room temperature and the data was analyzed by Malvern Dispersion Technology Software 4.20. Fluorescence measurements were carried out on a F97pro fluorescence spectrophotometer (Shanghai Lengguang industrial co ltd) with an excitation and emission slit width of 5 and 10 nm, respectively. UV-Vis spectra were obtained on a UV1700pc (Shanghai AuCy Scientific Instrument Co., Ltd) Ultraviolet spectrophotometer. Molecular weights of the samples were determined by Gel Permeation Chromatography (GPC) equipped with two columns (one Shodex GPC KD-804 column and one guard column), a refractive index detector (RID-10A), DMF was used as the mobile phase and the measurement was performed at 30 °C at a sample concentration of 3.0 mg/mL. Monodispersed polystyrene standards were used for the calibration of M_n, M_w and M_w/M_n.

Synthesis of Z-L-Lysine-NCA (lysine NCA 6)

Under a nitrogen atmosphere, 2g Z-L-Lys(Z)-OH and 2.1g triphosgene were suspended in 30ml dry THF. The reaction maintain at 45^{o}C and the mixture turned clear within 2h, then 70 ml dry n-hexane was added droplet into the solution at 0^{o}C. Next obtained white precipitation was recrystallized from THF/n-hexane twice.[17]

Synthesis of diblock polymer PEG-PZLL

0.6g mPEG-NH_2 was dissolved in 8ml anhydrous DMF in a flame-dried Schlenk flask filled with argon. 1.38g lysine NCA was dissolved in 5.0 ml anhydrous DMF and then added into the macroinitiator solution. The reaction was performed at 0°C for 3days. Then the solution was dialyzed against deionized water for 1days. 1.5g PEG-PZLL was obtained after Freeze-Drying.[17] ^{1}H-NMR (300MHz d_6-DMSO), δppm: 7.30(m, 64H), 4.96(m, 25H), 3.51(m, 174), 3.24(s, 3H), 2.94(m, 23H), 1.37(m, 72H).

Synthesis of L-Cystine NCA (cystine NCA 8)[17]

The synthesis of L-Cystine NCA monomer was according to the Reference 17. ^{1}H-NMR (300MHz d_6-DMSO), δppm: 4.78(t, 1H), 2.95(dd,1H), 3.02(dd, 1H).

Synthesis of mPEG-PLL$_{arm}$-PLC$_{core}$CCS Polymer(10)

460mg PEG-PZLL and 282.5mg Cystine NCA was dissolved in 15 ml anhydrous DMF. The reaction was performed at 40 °C for 3 days. Then the solution was dialyzed against deionized water for 1 day and powder was obtained after it was freeze-dried. The product was then dissolved in a mixture of 8 ml CF_3COOH and 2 ml HBr–acetic acid (33wt%). Next the solution was stirred for 1h at room temperature and then excess diethyl ether was poured into the solution to precipitate the polymer. The final nanogel was obtained by centrifugation and washed twice with diethyl ether.

Synthesis of 5-bromo-2,3,3-trimethylindolenine[29]

The synthesis was according to the method reported in Ref.29, and the product was measured by means of 1H-NMR(300MHz, CDCl3), δppm: 7.40(m,2H), 7.37(s,1H) 2.28(s, 3H), 1.27(s, 6H).

1-(5-Carboxypentyl)-5-bromo-2,3,3-trimethylindolenium(2)17 3.0g 5-bromo-2,3,3-trimethylindolenine and 2.4 g 6-bromohexanoic acid were dissolved in 20 mL of acetonitrile. The mixture was heated at 90 oC under N2 for 40h. Excess diethyl ether was added after the reaction, and the oily precipitation was washed by diethyl ether to afford 1.2g deep wine solid (22.8%). 1H-NMR(300MHz, d_6-DMSO) δppm: 8.19(s, 1H), 7.97(d, J=9Hz,1H), 7.87(d, J=9Hz,1H), 4.43(t, J=7.5Hz, 2H), 2.82(s, 3H), 2.22(t, J=7.5Hz, 2H), 1.82(m 2H), 1.54(m 8H), 1.42(m 2H)[30].

Synthesis of 2-Chloro-1-formyl-3-(hydroxymethylene)cyclohex-1-ene(4)[17]

The synthesis was according to the method reported in Ref.17. ^{1}H-NMR(300MHz, d_6-DMSO) δppm: 10.82 (s, 1H), 2.33 (overlap, 4H), 1.80−1.43 (m, 2H).

Synthesis of cyanine(5)

The mixture of 3 (1.2 g, 2.7 mmol), 4 (0.229 g, 1.32 mmol) and sodium acetate (0.22 g, 2.7 mmol) was heated at 70 °C for 1 h in the present of N_2 and anhydrous acetic anhydride (24 ml) to afford the cyanine. The green solution was cooled in air, and then it was poured into 100 ml saturated sodium bromide solution. The green solid was centrifuged and collected. Pure product (0.48g) was obtained by purification on silica gel column (ethylacetate and ethanol). ^{1}H-NMR(300MHz, $CDCl_3$) δppm: 8.26(d, J=15, 2H), 7.48(m, 4H), 7.05(d, J=9Hz, 2H), 6.19(d, J=15Hz, 2H), 4.07(t, J=7.5Hz, 3H), 2.67(m, 4H), 2.42(t, J=6Hz, 2H) 1.95(m, 2H) 1.75(m, 20H), 1.50(m, 4H).

Cyanine-loaded nanogel, and drug release

For cyanine-loaded nanogel, 27mg cyanine and 103mg nanogel were dissolved in 5 ml of DMF, and then it was stirred for 8h under darkness. The result solution was dialyzed against deionized water for 24h and renewed six times. At last, the solution was centrifuged and freeze-dried, to yield cyanine-loaded nanogel. UV-Vis measurement was applied to measure the DLC (drug loading content) and DLE drug loading efficiency was calculated according to following equations:

$$\mathrm{DLC(wt\%)} = \left(\frac{weight\ of\ loaded\ drug}{weight\ of\ nanogel}\right) \times 100\%$$

$$\mathrm{DLE(wt\%)} = \left(\frac{weight\ of\ laded\ drug}{weight\ of\ \mathrm{drug\ fed}}\right) \times 100\%$$

***In Vitro* cytotoxicity assay**

In a 96-well plate, Hepg2 cells were seed at a density of 5000 cells per well and incubated for 12 h. After cell stabilization, culture medium was replaced with 100 μl of medium containing cyanine, cyanine-loaded nanogel at various concentrations or completely DMSO (as control). After 4 h of incubation under dark, the cells were washed with PBS, and then fresh medium was added. The cells were immediately light irradiated or not (cells were irradiated at a height of 20cm for 5 min, and the laser output power was estimate 200 mW/cm^2).[28] The cell was incubated for another 5h and viability was evaluated by MTT assay.

Conclusions

Here, a biodegradable polypeptide nanogel has been synthesized which could be disassembled by GSH. A novel cyanine dye Br_2-IR808 has also been developed, which showed both high quantum yield for singlet oxygen generation and fluorescence in the NIR region. The nanogel was then loaded with a cyanine dye, and the nanogel is suitable for EPR and can control the release of drug by a reduction-responsive disassembly. Moreover, the cyanine-loaded nanogel exhibits better phototoxicity than free cyanine, and the amount of photosensitizer can be reduced from 30 μM to 2μM when the nanogel was utilized. The strong fluorescence of cyanine-loaded nanogel makes it possible for NIR imaging. All these advantages make cyanine-loaded nanogel as a potential agent for future tumour imaging and PDT therapy.

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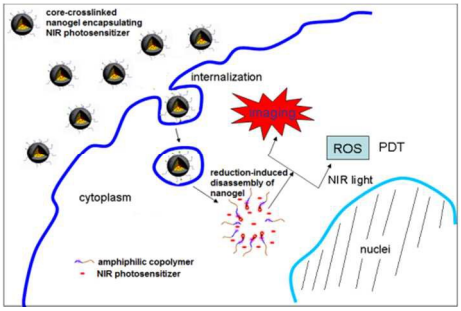
Polymer Chemistry

ARTICLE

Table of contents

Reduction-responsive Polypeptide Nanogel Encapsulating NIR Photosensitizer for Imaging Guided Photodynamic Therapy

Titao Jing, Liyi Fu, Le Liu, Lifeng Yan*



Internalization of the core-crosslinked nanogel containing NIR photosensitizer followed by reduction-induced release for both imaging and PDT.1