Preparation and investigations of PEG-AT-PEG organic nano-polymer photothermal material

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Abstract
Conjugated polymer (CPs) has good near infrared (NIR) absorption and high photothermal conversion effect, which is one of the most promising photothermal therapy (PTT) drugs for cancer therapy. Through the combination of hydrophobic conjugate component of aniline trimer (AT) and hydrophilic component of aldehyde polyethylene glycol (PEG-CHO), linear polymer (PEG-AT-PEG) is synthesized via Schiff base reaction. Self-assembly nanoparticles simply precipitated out by dropping the tetrahydrofuran solution of PEG-AT-PEG into deionized water under ultrasonic dispersion. Owing to the rigid hydrophobic conjugated structure in the middle and the hydrophilic long chain structure at both ends, the long chain material can undergo hydrophobic association and π−π stacking in deionized water to form spherical organic nanoparticle. Such self-assembly nanoparticles have strong NIR absorption at 700 ~ 800 nm, and can significantly increase the temperature in a short time upon continuous 808 nm laser irradiation, showing good photothermal conversion efficiency. The nanoparticles of PEG-AT-PEG show good biocompatibility to Hela cells at low concentration, when exposed to laser light, the destruction of Hela tumor cells was very distinct in the concentration range of 200 to 800 μg mL⁻¹. Synthetic strategy based on CPs will be possible to develop more effective nanomaterials for treating cancer or tumors.

1. Introduction

Cancer is considered one of the deadliest diseases of the 21st century for human beings [1, 2]. At present, cancer is usually treated by surgery, chemotherapy and radiotherapy in the clinic. Although the traditional treatments are effective, shortcomings still exist, such as internal injury, serious side effects, high cost and reduced therapeutic effect, etc. Photothermal therapy (PTT) is a new method of treating cancer cells by injecting photothermal agents (PTAs) with high photothermal conversion efficiency into the human body, then PTAs converts received light energy into heat to kill cancer cells [3]. Compared with traditional cancer therapies, PTT is a non-invasive therapeutic intervention, which possesses many advantages, e.g. high efficiency, spatial specificity and remote control capability [4–6]. In recent years, an increasing number of researchers are paying attentions to synthesis of effective PTAs with significant characteristics, such as high absorbance rate of near infrared (NIR) light [7], high photothermal conversion efficiency [8, 9], appropriate size [10], excellent biocompatibility and low cytotoxicity [11, 12].

Currently, numerous PTAs have been well-studied. They are mainly divided into inorganic and organic types. Among the inorganic PTAs, metal-based nanomaterials (Au, Ag, Pd and Ge), especially gold-based nanomaterials have been extensive researched owing to their high thermal conversion efficiency and biological inert property [13]. Carbon-based nanomaterials, including quantum dots [14], carbon nanotubes [15], graphene and their derivatives [16], are also popular candidates because of the considerable thermal conversion...
efficiency. Nevertheless, the developments and applications of inorganic PTAs are significantly limited by their complicated synthesizing procedures, high cost and reduced optical stability [17, 18]. The polymers with the π–π conjugate structure in a wide range are the prominent representatives of organic PTAs. Compared with inorganic PTAs, organic PTAs generally possess the advantages of the biodegradability, low toxicity, desirable photothermal conversion efficiency and high photostability [19].

To date, poly-(3,4-ethylene dioxythiophene):poly(4-styrenesulfonate) (PEDOT:PSS), poly[9,9-bis(4-(2-ethylhexyl)phenyl)fluorene-alt-co-6,7-bis(4-(hexyloxy)phenyl)–4,9-di(thiophen-2-yl)-thiadiazoloquinolinoxaline] (PFTTQ), polypyrrole (PPy), dopamine–melanin, and polyaniline nanoparticles have been proved to have remarkable photothermal effect [19]. Liu and his workers prepared a specific polymeric PTAs, which was derived from PEDOT:PSS, the PTAs with a diameter of 80 ~ 90 nm exhibited excellent PTT efficiency [20]. Polyaniline has the advantages of low cost, low toxicity to cells and significant near infrared absorption, which has a good potential in organic photothermal therapy materials. There was considerable evidence showed that polyaniline can be used as a suitable PTA for PTT applications. Haam and his team synthesized polyaniline-based nanoparticles via chemical oxidation polymerization method. The obtained water-soluble polyaniline nanoparticles exhibited good colloidal stability and NIR absorption [21]. Li and his coworkers synthesized uniform polyaniline nanoparticles through a hydrothermal method and the product is further coated with polyoxyethylene chains. The modified polyaniline nanoparticles showed some advantages, such as appropriate size, excellent water solubility, good NIR absorbance rate, etc [22]. Compared with polymers, conjugated polymers and their derivatives are more attractive for biomedical applications because of their biodegradability and ease of synthesis. Among aniline oligomers, aniline trimer (AT) is easily synthesized, and the electrical and optical properties of AT are comparable with polyaniline [23–26]. As far as we know, the application of AT as PTAs for PTT have not been reported. However, poor water solubility and possible biological cytotoxicity of AT are the biggest factors restricting its application and research as phototherapy reagent.

In this paper, we designed a new organic linear polymer based on photothermal AT and biocompatible polyethylene glycol (PEG). As is known to all, PEG has good water solubility and conjugate polymer can improve its biocompatibility in photothermal therapy materials by modifying PEG derivatives, which have been some reports [27, 28]. We introduced PEG blocks at both ends of AT to solve the problem of water solubility and improve its biocompatibility, and further investigated its application in PTT. AT was first prepared through oxidative coupling of p-phenylenediamine and aniline. Then the presynthesized PEG aldehyde (PEG-CHO) was connected to AT by Schiff base synthesis to obtain final organic PEG-AT-PEG.

It has been proved that an effective method of transferring organic chlorinated paraffins to aqueous media is by precipitation. The chlorinated paraffins dissolved in tetrahydrofuran were precipitated into water to obtain NP suspension [29, 30]. The NPs have demonstrated good photostability and biocompatibility in biosensing and bioimaging applications. We prepare PEG-AT-PEG NPs by improving the reported method [28, 31]. Specifically, PEG-AT-PEG tetrahydrofuran solution is directly dropped into deionized water under ultrasonic dispersion to obtain PEG-AT-PEG nanoparticle suspension.

We proved the successful synthesis of PEG-AT-PEG linear polymer by the characterization of 1H NMR and IR spectra. The photothermal effect of PEG-AT-PEG NPs has been studied via observing the solution temperature change with 808 nm laser irradiation. The temperature of PEG-AT-PEG NP solution increased frequently from 25 °C to 50 °C at a concentration of 0.5 mg ml⁻¹ (0.5 W cm⁻², 3 min). This indicates that the material has good photothermal conversion efficiency and has the potential to be used in photothermal therapy to inhibit tumor cells. Moreover, we cultured PEG-AT-PEG NPs together with Hela cells and found that they have good biocompatibility, and used laser irradiation to investigate the therapeutic effect of the material, and found that at concentrations above 200 mg ml⁻¹, PEG-AT-PEG NPs can significantly inhibit Hela tumor cells. Both photothermal conversion studies and in vitro studies have shown that PEG-AT-PEG NPs is an effective PTT reagent.

2. Materials and methods

2.1. Chemicals

Amino PEG hydroxyl (PEG-NH₂, Mw:1000Da), 4-formylbenzoic acid (ar, 98%), N-Hydroxy succinimide (NHS, ar, 98%), N-(3-Dimethylaminopropyl)-N'-ethyl carbodiimide hydrochloride (EDC-HCl, ar, 99%), p-phenylenediamine (ar, 99%), aniline (ar, 99%), ammonium persulphate (NH₄)₂S₂O₈, ar, 98%) and Sodium borohydrate (NaBH₄, ar, 98%) were purchased from Aladdin (Shanghai, China). Fetal bovine serum (FBS), Dulbecco’s modified Eagle’s medium (DMEM), Dimethyl sulfoxide (DMSO) and tetrahydrofuran (THF) were also supplied by Sigma-Aldrich. Hela cells were purchased from Shanghai Zhong Qiao Xin Zhou Biotechnology Co.Ltd. (Shanghai, China). All chemicals were used without additional purification.
2.2. Preparation of PEG-CHO
Amino PEG hydroxyl (PEG-NH₂, 50.0 mg) and 11.2 mg of 4-formyl benzoic acid were dissolved in a mixture of dimethyl sulfoxide (DMSO) and water (15 ml, 1:2, v/v). Then 9.1 mg of NHS and 14.5 mg of EDC · HCl were added and stirred at room temperature for 24 h. After that, DMSO and other components were removed through the dialysis bag (MWCO:1000). The resulting solution was freeze-dried to yield PEG-CHO.

2.3. Preparation of aniline trimer (AT)
AT was prepared according to articles reported [32]. In brief, AT was synthesized via oxidative coupling of p-phenylenediamine and equivalent amounts of aniline with equivalent amounts of (NH₄)₂S₂O₈ as oxidant.

2.4. Synthesis of PEG-AT-PEG
PEG-CHO (1.15 g) and AT (0.29 g) were stirred in 30 ml of THF at room temperature. The mixture was allowed to react for 10 min. Then NaBH₄ (0.080 g) was added into the mixture, and the reaction was carried out for 0.5 h to obtain PEG-AT-PEG. Afterwards, THF and extra components were removed by the dialysis bag (MWCO:1000). The obtained solution was freeze-dried to obtain dry PEG-AT-PEG.

2.5. Preparation of PEG-AT-PEG NPs
PEG-AT-PEG NPs were prepared by a modified precipitation method according to previous reports [28, 31]. A THF solution containing PEG-AT-PEG matrix was transferred to water under sonication. The NP suspension was obtained with stirring overnight. The NP suspension was filtered by a 0.2 μm syringe filter to obtain PEG-AT-PEG NPs.

2.6. Cytotoxicity of PEG-AT-PEG NPs
Cell viability of Hela cells was detected by cell counting kit-8 (CCK-8). In brief, Hela cells were inoculated in 160 μl 96-well microplates containing 10% fetal bovine serum at a density of 4 × 10⁴ cells per ml⁻¹. the cells were incubated with various concentrations of PEG-AT-PEG NPs for 24 h. Then PEG-AT-PEG NPs were removed and cells were washed with phosphate buffer solution three times. 10 μl of CCK-8 dye and 100 μl of DMEM cell culture medium were added to each well and incubated for 2 h. After that, the sample was measured with a microplate reader and the absorbance at 450 nm was recorded. These values are positively correlated with the number of living cells. Three repeat holes were used for each microporous plate, and the experiment was performed for 3 times. Cell survival was expressed as absorbance relative to untreated control. The result values are expressed as mean ± standard deviation.

2.7. Hela cancer cells suppression study of PEG-AT-PEG NPs
Cell viability of Hela cells was detected by cell counting kit-8 (CCK-8). Hela cells were inoculated in 160 μl 96-well microplates containing 10% fetal bovine serum at a density of 4 × 10⁴ cells per ml⁻¹. the cells were incubated with various concentrations of PEG-AT-PEG NPs and the selected wells were exposed to 808 nm laser at 0.5 W cm⁻² for 10 min. After laser exposure, the cells were further cultured for 24 h. Then PEG-AT-PEG NPs were removed and cells were washed with phosphate buffer solution three times. 10 μl of CCK-8 dye and 100 μl of DMEM cell culture medium were added to each well and incubated for 2 h. After that, the sample was measured with a microplate reader and the absorbance at 450 nm was recorded. These values are positively correlated with the number of living cells. Three repeat holes were used for each microporous plate, and the experiment was performed for 3 times. Cell survival was expressed as absorbance relative to untreated control. The result values are expressed as mean ± standard deviation.

2.8. Characterization
The samples were analyzed through transmission electronic microscopy (TEM), Fourier-transform infrared (FTIR) spectroscopy. UV–vis absorption spectra were recorded with a Perkin Elmer LAMBDA35 UV/vis spectrophotometer. ¹H NMR were recorded on a BRUKER 400 MHz spectrometer in CDCl₃. Chemical shifts were reported referenced to an internal tetramethylsilane standard or the CDCl₃ residual peak for ¹H NMR. TEM samples were prepared via dispersing the sample on a carbon-coated copper grid to evaporate the excess solvent. The TEM images were recorded on the Hitachi 7650B microscope operated at 120 kV. FTIR spectra were recorded on a Nicolet 380 Fourier transform spectrometer. Photothermal data in PEG-AT-PEG solution were obtained through a FLIR E40 device running on a FLIR tool system in conjunction with an 808 nm laser. Dilutions of PEG-AT-PEG NPs in water (0.1, 0.25, 0.5, 0.75, 1.0 and 2.0 mg ml⁻¹) were put in various specimen bottles irradiated by 808 laser exposure (0.5 W cm⁻²). Temperature values were recorded at different time intervals using FLIR tool systems.
3. Results and discussions

3.1. Synthesis of PEG-AT-PEG
AT, PEG-CHO, PEG-AT-PEG were synthesized through the synthetic route shown in Scheme 1. The structure of PEG-AT-PEG is also shown in Scheme 1, which contains a hydrophobic unit and a hydrophilic unit. First, we selected the monomer AT as the energy absorption block of the photothermotherapy polymer, we found that the structure of AT has a certain degree of electron deficiency and exhibits a good absorption from 700 to 800 nm based on this work. At the same time, the extremely poor hydrophilic properties of monomeric AT also provide necessary conditions for the subsequent preparation of nanoparticles. Then, in order to improve the cytocompatibility and hydrophilicity of AT, we chose PEG (PEG-NH₂, Mw:1000Da) as the hydrophilic block of the photothermotherapy polymer, which has been reported to improve biocompatibility in several literatures [33, 34]. Finally, we synthesized PEG-AT-PEG linear oligomeric by Schiff base reaction. Self-assembly nanoparticles simply precipitated out by dropping the tetrahydrofuran solution of PEG-AT-PEG into deionized water under ultrasonic dispersion.

PEG-AT-PEG NPs are a spherical core–shell structure containing an intermediate core AT providing photothermal effects and an outer layer of PEG improving biocompatibility. in which the intermediate core conjugated structure having rigidity and hydrophilicity easily produces aggregation via hydrophobic interactions and π–π stacking effect and the flexible and water-soluble PEG at both ends wraps around the surface of the hydrophobic core to form core–shell nanoparticles. Compared with other completely dissolved PTAs, the suspended particles can block a part of the laser light, coupled with the electron-deficient nature of the block AT conjugated, which has certain design advantages in photothermal conversion efficiency. The modification of PEG can improve the biocompatibility of photothermal therapy materials in inorganic photothermal therapy materials and conjugated organic photothermal therapy materials. In this paper, the PEG introduced at both
ends has two potential advantages. On the one hand, it can effectively promote the dissolution and ensure that the photothermal block AT can be better absorbed. On the other hand, the long-chain hydrophilic PEG at both ends will inevitably be entangled or wrap the middle hydrophobic block AT, which is beneficial to the stability of PEG-AT-PEG NPs (figures 2(b), (c)). moreover, it is worth noting that the PEG-AT-PEG synthesized in this paper is a linear polymer with a small molecular weight, which can form small organic nanoparticles (∼7 nm), a small-sized photothermotherapy material, which is very beneficial to the endocytosis of cells, and it is another good advantage of the material.

Figure 1(a) shows the $^1$H NMR spectra of PEG, PEG-CHO, and PEG-AT-PEG. We can see that the three materials all have the same and strong signal peak at 3.5 ppm, which is the signal peak of the PEG backbone, indicating that all three materials contain PEG. From the spectrum of PEG-CHO, a signal peak at 10.1 ppm can be seen, which is the signal peak of aldehyde group, indicating that 4-formylbenzoic acid was successfully linked to PEG. In the spectrum of PEG-AT-PEG, the peak at 10.1 ppm disappears, indicating that the aldehyde group has reacted, and the signal peak of amine at 8.8 ppm appears, which proves that AT successfully reacts with the PEG block, which in turn proves that PEG-AT-PEG The polymer synthesis was successful.

3.2. Self assembly of PEG-AT-PEG NPs
PEG-AT-PEG NPs were prepared by simply dropping PEG-AT-PEG tetrahydrofuran solution into deionized water precipitation under the action of ultrasound. The hydrophobic AT segments were easily entangled by the hydrophilic PEG chains. Due to the rigid hydrophobic conjugated structure in the middle and the hydrophilic long chain structure at both ends, the long chain material can undergo hydrophobic association and π–π stacking in deionized water to form organic nanoparticles. PEG-AT-PEG NPs (prepared by tetrahydrofuran solution of 0.5 mg ml$^{-1}$ PEG-AT-PEG) represent an average size of 7 nm (figures 2(a), (b)). PEG-AT-PEG NPs size did not change significantly during continuous observation at room temperature in 10 days (figure 2(c)), indicating the excellent the nanoparticles stability. moreover, the size of PEG-AT-PEG NPs can be easily
controlled by changing the PEG-AT-PEG concentration at the original. The capability of PEG-AT-PEG NPs size to be fine-tuned is very conducive to expanding its range of applications.

Figure 3 (a) exhibits the UV–vis absorption spectrum of PEG-AT-PEG NP suspensions in water. The absorption peak at 425 nm is derived from $\pi-\pi^*$ transition of the conjugated backbone, while the absorption band from 700 to 800 nm results from charge transfer between tribiphenylamine (figure 3 (b)). Notably, PEG-AT-PEG NPs had almost no significant fluorescence at 725 nm, illustrating that most of the received energy is generated through a non-radiative transition back to the ground state, and it also indicates that the material has good photothermal conversion effect.

3.3. Photothermal Performance

The temperature change of PEG-AT-PEG NP suspensions at different concentrations (808 nm laser, 0.5 W cm$^{-2}$). As exhibited in figure 4(a), the temperature increase upon exposure reaches a steady state at 120–160 s, and the temperature of 0.5 mg ml$^{-1}$ PEG-AT-PEG NPs rises from 25 °C to 50 °C on laser exposure in 3 min. In contrast, the temperature of water only rises from 25 °C to 31 °C. Besides, the temperature rises with the increase in the concentration of PEG-AT-PEG NP suspensions (figure 4(b)). Reported articles have demonstrated that the temperature rise in the range of 15 °C ~ 20 °C within 5 min can cause a lot of damage to tumor tissue [9, 19]. Considering that good photothermal effect is very beneficial to tumor cell suppression, the selection of appropriate photothermal material concentration is very important for cancer treatment and patient’s health.

3.4. Toxicity and inhibition test of PEG-AT-PEG NPs on Hela cells

The biocompatibility of PEG-AT-PEG NPs has been evaluated using Hela cells. As shown in figure 5(a), After PEG-AT-PEG NPs was incubated in a concentration below 200 µg ml$^{-1}$ for 24 h, the cells exhibited no obvious cytotoxicity and the cell viability remained above 80%. Even at 400 µg ml$^{-1}$, the survival rate of Hela cells was...
still above 70% (Figure 5(A)), indicating that PEG-AT-PEG NPs had good biocompatibility. Owing to further study the PTT effect of PEG-AT-PEG NPs, Hela cells incubated with NPs were treated in laser exposure, and the cell viability was exhibited in Figure 5(b). The cell viability declined rapidly after laser exposure. More than 65% of Hela cells were destroyed upon incubation with the concentration of 400 μg ml⁻¹ PEG-AT-PEG NPs, showing that had significant suppression and destructive effects for Hela cells. These results proved that the NPs has a good therapeutic effect under laser irradiation in vitro.

4. Conclusions

We developed an organic linear polymer PEG-AT-PEG successfully synthesized by Schiff base-catalyzed reaction. The linear polymer contains a rigid hydrophobic unit in the middle and two hydrophilic flexible long-chain units at both ends. This structure can be easily hydrophobic association and π–π stacking occurred in deionized water to form spherical organic nanoparticles. We prepared spherical PEG-AT-PEG NPs by an improved simple precipitation method, and carried out photothermal conversion studies on them. It was found that the self-assembled nanoparticles had strong near-infrared absorption at 700 ~ 800 nm, and the laser exposure for 3 min, the temperature of the PEG-AT-PEG NP suspensions (0.5 mg ml⁻¹) could be quickly rise from 25 °C to 50 °C, with good photothermal conversion efficiency. After electron microscopy and particle size analysis, we were pleasantly surprised to find that the average size of this organic nanoparticle is only 7 nm, which is very beneficial for cell endocytosis, drug absorption, and reducing drug residual damage. More notably, when we performed in vitro experiments, it was found that PEG-AT-PEG nanoparticles exhibited good biocompatibility to HeLa cells at low concentrations, While under laser irradiation, effective cancer cell killing was observed in the concentration range of 200 to 800 μg ml⁻¹. At a concentration of 600 mg ml⁻¹, More than 75% of Hela cells were damaged. It has a good inhibitory effect on Hela tumor cells, which indicates that PEG-AT-PEG NPs have great potential as PTA.

Data availability statement

All data that support the findings of this study are included within the article (and any supplementary files).

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Conflicts of interest

The authors declare no conflict of interest.
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