

Non-covalently Functionalized Carbon Nanotube by Hyaluronic Acid Based Azo Polymer for Photothermal Elimination of Tumor Cells

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 Electronic Supplementary Information

Abstract Photothermal therapy has been renowned for its non-invasive and highly precise approach in cancer treatment. Therefore, the synthesis of suitable photothermal agent has attracted wide attention. In this study, a non-covalent method for modifying carbon nanotube by hyaluronic acid based azo polymer was proposed. Hyaluronic acid based azo polymer was attached to the surface of carbon nanotube *via* the π - π interaction and hydrophobic interaction between azo moiety and the wall of carbon nanotube. After the self-assembly process, the modification was demonstrated with transmission electron microscopy, infrared spectra and thermal gravimetric analysis. The modified carbon nanotube (HA-MWCNT) was endowed with both the tumor cell targeting property of hyaluronic acid and the excellent photothermal effect of carbon nanotube, enabling it to serve as photothermal agent for eliminating tumor cells. Upon co-culture with HeLa cells, HA-MWCNT was proved to exhibit low cytotoxicity without irradiation. After being irradiated with infrared laser light, the HeLa cells cultured with HA-MWCNT perished due to the heat generated by the endocytosed HA-MWCNT, which attested to the potential of HA-MWCNT as a photothermal agent for cancer treatment.

Keywords Azobenzene; Hyaluronic acid; Carbon nanotube; Photothermal therapy

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INTRODUCTION

Cancer remains one of the most fatal diseases endangering human life.^[1–3] For decades, researchers have devoted themselves to the development of cancer treatments, the most widely used of which are surgery, chemotherapy, and radiotherapy.^[4] However, the shortcomings of these treatments, such as surgical trauma, drug resistance, and severe side effects, pose threats to the survival and prognosis of patients.^[5] As a promising non-invasive cancer treatment with high precision, photothermal therapy, which converts light into heat using photothermal agents and thus leads to cell death, has drawn extensive attention.^[6–8] A variety of photothermal agents, including metal oxide nanomaterials^[9] conjugated polymer,^[10,11] and carbon nanomaterials^[12] have been developed to target tumors and perform photothermal therapy with high efficiency.

Carbon nanotubes (CNTs) have been widely applied as photothermal agents owing to their wide absorption bandwidth and excellent photothermal conversion characteristics.^[13–15] However, owing to their large specific surface area and high aspect ratio, pristine carbon nanotube display poor dispersion in water and other solvents, thereby

limiting their biomedical application as photothermal agents.

To disperse carbon nanotubes and deliver them to the tumor site for photothermal therapy, both covalent^[16,17] and non-covalent^[18–20] surface modifications have been carried out, among which non-covalent modification by amphiphilic polymers is a convenient approach because of its high efficiency and mild conditions. Azobenzene has a large conjugated structure that can adhere to the surface of carbon nanotube through π - π interactions, making it feasible for carbon nanotube dispersion.^[21–23] Hence, azobenzene could be employed as a hydrophobic component in constructing amphiphilic polymers to enhance the water dispersion of carbon nanotubes. With excellent water solubility, good biocompatibility, and biodegradability, hyaluronic acid is also known to target CD44 receptors that are overexpressed on the surface of tumor cells, rendering it suitable as a targeting delivery vector for tumor cells.^[24–26]

Consequently, combining hyaluronic acid as the hydrophilic segment with azobenzene as the hydrophobic part to produce the amphiphilic hyaluronic acid-based azo polymer would not only disperse carbon nanotube but also bestow them with tumor cell-targeting properties. The dispersion of carbon nanotube depends on the grafting ratio of the azo moiety on the hyaluronic acid backbone. Grafting azobenzene onto hyaluronic acid *via* direct amidation or esterification reactions might result in a relatively low grafting ratio because of the solubility and steric hindrance of azobenzene^[27,28], which would lead to a lack of π - π interaction

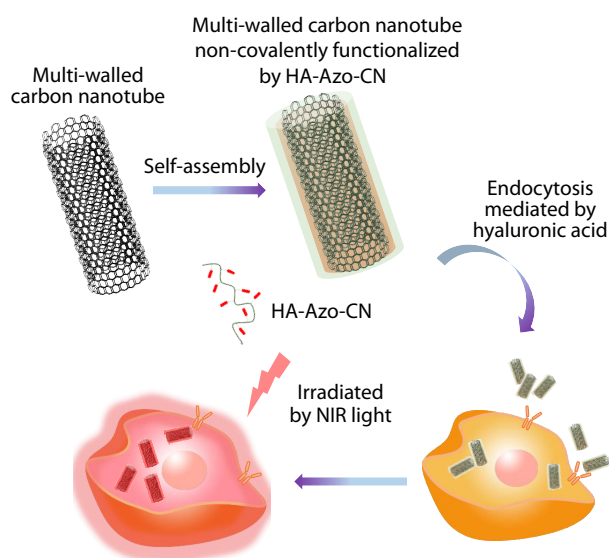
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and poor dispersion of carbon nanotube. To increase the grafting ratio, we designed a new strategy to synthesize hyaluronic acid-based azo polymers by integrating transesterification and post-azo coupling reactions.^[29] With a hyaluronic acid-based azo polymer with a high grafting ratio, the non-covalently modified carbon nanotube would possess good water dispersion and be able to target tumor cells, which would further promote the effectiveness of photothermal therapy.

In this study, we synthesized a hyaluronic acid-based azo polymer (HA-Azo-CN) *via* transesterification and a subsequent post-azo coupling reaction with 4-aminobenzonitrile. As illustrated in Scheme 1, following the self-assembly procedure, HA-Azo-CN was attached to multi-walled carbon nanotube (MWCNT) *via* π - π interaction and hydrophobic interaction, thereby producing HA-modified MWCNT (HA-MWCNT). HA-MWCNTs were then co-cultured with HeLa cells, and cell viability was evaluated with and without infrared light irradiation to validate the photothermal effect on tumor cells.



Scheme 1 The fabrication of HA-MWCNT and HA-MWCNT functioning as photothermal agent in the elimination of tumor cells.

EXPERIMENTAL

Materials and Methods

N-Ethyl-*N*-hydroxyethylaniline (99%), sodium nitrite (99%), and tetrabutylammonium hydroxide (40% W/W in water) were purchased from Meryer. 4-Toluenesulfonyl chloride (99%), 4-aminobenzonitrile (99%), and potassium hydroxide (85%) were purchased from J&K Scientific. Sulfuric acid was purchased from TGREAG. Hyaluronic acid (MW 8×10^5 – 1×10^6) was purchased from Heowns. Dimethyl sulfoxide was purchased from Acme. Multi-walled carbon nanotubes (diameter: 30–50 nm, length: 0.5–2 μ m) were purchased from XFNano. Dulbecco's Modified Eagle Medium (DMEM) was purchased from Pricella. The double-staining kit was purchased from APEXIO Technology LLC.

¹H-NMR spectra were measured using a JEOL spectrometer (JNM-ECZ400S). UV-Vis spectra were measured using an Agilent Cary 300 UV-Vis spectrophotometer. Images of the HeLa

cells were captured using a Nikon Ti2-E CLSM confocal laser scanning microscope. TEM images were captured using a HITACHI TEM (H7650B) instrument. Thermogravimetric experiments were performed using a Mettler-Toledo TGA/DSC 1/1100 system. Fourier transform infrared (FTIR) spectra were obtained using a Thermo Nicolet 6700 FTIR spectrometer.

Synthesis of *N*-(4-methyl ethylbenzenesulfonate)-*N*-ethyl-aniline (NBNE)

4-Toluenesulfonyl chloride (4.31 g) and *N*-ethyl-*N*-hydroxyethylaniline (3.40 g) were dissolved in tetrahydrofuran (70 mL) in an ice water bath before the KOH aqueous solution (0.29 g/mL) was added dropwise. After stirring for 24 h, the mixture was poured into petroleum ether (600 mL). Then, the mixture was extracted with a saturated sodium chloride aqueous solution before it was further dried with anhydrous magnesium sulfate. After cooling crystallization at -30 °C for 24 h, a white solid was collected in 79% yield.

Synthesis of Tetrabutylammonium Salt of Hyaluronic Acid (HA-TBA)

Hyaluronic acid (MW 8×10^5 – 1×10^6 , 2.82 g) was dissolved in deionized water (200 mL) before the addition of tetrabutylammonium hydroxide (40% W/W in water, 15 g). The mixture was stirred for 24 h and then transferred to a dialysis bag (3500 Da) to remove extra tetrabutylammonium hydroxide. After dialysis for 2 days, the solution was freeze-dried, and a white solid was collected in 70% yield. The ¹H-NMR spectrum was shown in Fig. S1 (in the electronic supplementary information, ESI). ¹H-NMR (400 MHz, D₂O, δ): 0.81 (t, $-\text{CH}_3$), 1.23 (m, $-\text{CH}_2$), 1.51 (m, $-\text{CH}_2$), 1.88 (s, $-\text{CH}_3$), 3.02–3.81 (br, $-\text{CH}$, $-\text{CH}_2$).

Synthesis of Hyaluronic Acid Grafted with *N*-Ethyl-*N*-hydroxyethylaniline (HA-NE)

HA-TBA (2.22 g), K₂CO₃ (4.31 g), and NBNE (5.30 g) were successively added to dimethyl sulfoxide (140 mL). After stirring for three days at room temperature, the solution was poured into a mixture of petroleum ether and ethyl acetate (1:1) to extract dimethyl sulfoxide. The bottom layer was then transferred to a dialysis bag (3500 Da). After dialysis for 2 days, the solution was freeze-dried, and a yellow solid was collected in 23% yield. ¹H-NMR spectrum was shown in Fig. S2 (in ESI), the grafting ratio of *N*-ethyl-*N*-hydroxyethylaniline was 93%. ¹H-NMR (400 MHz, DMSO-*d*₆, δ): 1.79 (m, $-\text{CH}_3$), 6.00–4.97 (br, $-\text{CH}$, $-\text{CH}_2$, $-\text{OH}$), 6.55 (m, $-\text{Ar H}$), 6.66 (m, $-\text{Ar H}$), 7.15 (m, $-\text{Ar H}$).

Synthesis of Hyaluronic Acid Grafted with Azobenzene (HA-Azo-CN)

Aminobenzonitrile (0.41 g) was dissolved in acetic acid (8.4 mL), and sulfuric acid (0.84 mL) was added dropwise. Then, sodium nitrite aqueous solution (0.22 g/mL) was added to the mixture in an ice water bath until the white suspension turned light yellow. The light-yellow solution was added dropwise to HA-NE (0.46 g), which was dissolved in dimethyl sulfoxide (70 mL). After stirring for 24 h, the solution was poured into a mixture of petroleum ether and ethyl acetate (1:1) to extract the dimethyl sulfoxide. The bottom layer was then transferred to a dialysis bag (3500 Da). After dialysis for 2 days, the solution was freeze-dried, and the red solid was collected in 57% yield. ¹H-NMR spectrum was shown in Fig. S3 (in ESI), the grafting ratio of azo moiety was 66%. ¹H-NMR (400 MHz, DMSO-*d*₆, δ): 1.76 (m, $-\text{CH}_3$), 4.02–4.97 (br, $-\text{CH}$, $-\text{CH}_2$, $-\text{OH}$), 6.83 (m, $-\text{Ar H}$), 7.29–8.07 (br, $-\text{Ar H}$).

Preparation of Multi-walled Carbon Nanotube Non-covalently Functionalized by HA-Azo-CN (HA-MWCNT)

HA-Azo-CN (28 mg) and multi-walled carbon nanotube (28 mg) were added to dimethyl sulfoxide (10 mL). After sonication for 1 h, deionized water (20 mL) was added to the mixture at a rate of 20 mL/h. The solution was then transferred to a dialysis bag (3500 Da). After dialysis for 2 days, the solution was freeze-dried to obtain HA-MWCNTs.

Dispersion Stability Test of HA-MWCNT

The HA-MWCNTs were dispersed in DMEM at a concentration of 100 µg/mL by sonication for 1 h. The solution was then maintained. A UV-Vis spectrophotometer was used to observe the transmittance of the solution, which demonstrated the dispersion stability of HA-MWCNTs in DMEM.

Photothermal Capability Test of HA-MWCNT

The HA-MWCNTs were dispersed in DMEM (100 µg/mL) after sonication for 1 h. The solution was then irradiated with laser light (980 nm, 1.5 W/cm²) for 7 min to track the temperature increase before it spontaneously returned to room temperature. The temperature variation was recorded using a Fotric 223s infrared thermal camera.

Cell Culture and Cellular Uptake

HeLa cells were seeded in 96-well plates at a density of 2.5×10⁴ cells/well in DMEM (100 µL). After culturing at 37 °C for 8 h, HA-MWCNTs were added to the 96-well plate and co-cultured for 24 h at concentrations of 12, 16, 20, 24, 28, and 32 µg/mL, so that HeLa cells could intake HA-MWCNT sufficiently.

Photothermal Effect on HeLa Cells

After cell culture and cellular uptake of HA-MWCNTs, the supernatant was removed to eliminate the effect of HA-MWCNTs, which were not absorbed by HeLa cells. The 96-well plate was irradiated with laser light (980 nm, 1.5 W/cm²) for 7 min to perform photothermal elimination. A cytotoxicity assay was performed to determine the effect of photothermal elimination.

Cytotoxicity Assay

The cytotoxicity of HA-MWCNTs, both with and without laser light irradiation, was evaluated using the MTT assay. After cell culture and cellular uptake of HA-MWCNTs, both with and without laser light irradiation, the supernatant was replaced with MTT solution which was diluted with DMEM (10% V/V). After incubation for 4 h, the MTT solution was replaced with the Formazan solution. The absorbance was measured at 570 nm to determine cell viability.

Fluorescence Staining

Fluorescence staining was performed to assess the cell viability. Acridine orange and propidium iodide were used simultaneously to stain the cells after cell culture and cellular uptake of HA-MWCNTs, both with and without laser light irradiation. After staining, the fluorescence of HeLa cells was observed using confocal laser scanning microscope (λ_{ex} =488, 562 nm; λ_{em} =500–550 nm, 570–620 nm).

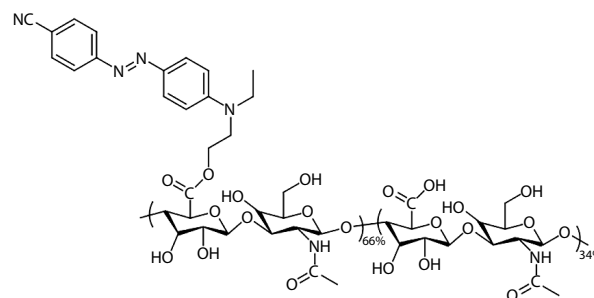
RESULTS AND DISCUSSION

Preparation and Characterization of HA-Azo-CN and HA-MWCNT

As illustrated in Scheme S1 (in ESI), HA-Azo-CN was synthesized

according to a previously reported procedure.^[29] As shown in Figs. S1–S3 (in ESI), ¹H-NMR spectra verified the structure of the product and grafting ratio. The grafting percentage of the azo moiety in HA-Azo-CN was 66%. The structure of HA-Azo-CN is shown in Scheme 2.

After obtaining HA-Azo-CN with a high grafting ratio, self-assembly was performed to produce HA-MWCNTs. MWCNT were dispersed in DMSO by sonication with HA-Azo-CN. Along with the addition of water, HA-Azo-CN was affixed to the surface of the MWCNT through π - π and hydrophobic interactions. The solution both before and after the self-assembly process was examined by UV-Vis spectroscopy, as illustrated in Fig. 1(a), and after the self-assembly process with MWC-



Scheme 2 The structure of HA-Azo-CN.

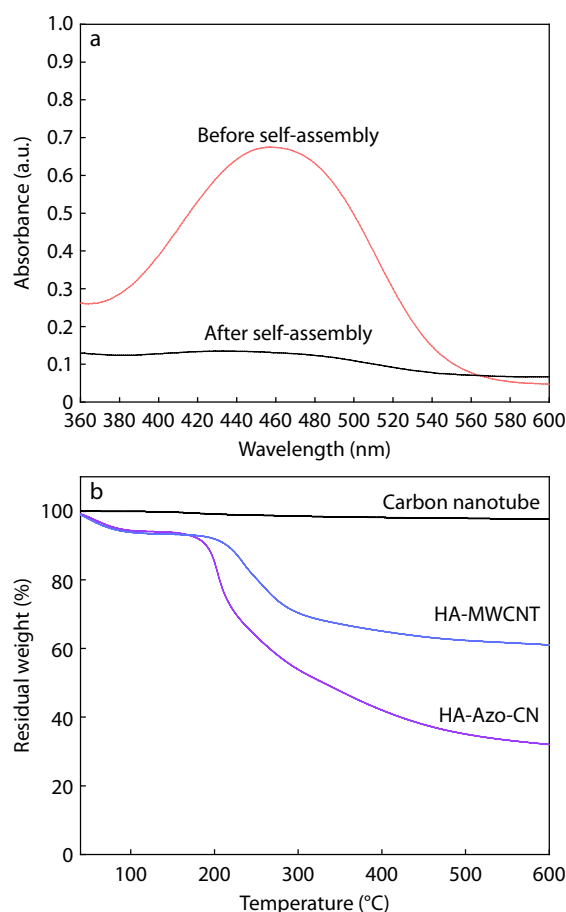


Fig. 1 (a) UV-Vis spectra of HA-Azo-CN solution both before and after self-assembly with MWCNT; (b) Thermogravimetric diagram of pristine carbon nanotube, HA-Azo-CN and HA-MWCNT.

NT, the peak of HA-Azo-CN at 460 nm almost disappeared, indicating that HA-Azo-CN was mostly attached to the surface of the MWCNT. To determine the ratio of modification, thermal gravimetric analysis was performed, as shown in Fig. 1(b). Calculated from the difference in weight loss among the carbon nanotube, HA-Azo-CN, and HA-MWCNT, the ratio of HA-Azo-CN attached to MWCNT was 95%.

As illustrated in Fig. 2(a), infrared spectroscopy was employed to characterize the HA-MWCNTs. HA-MWCNT demonstrated peaks that belonged to HA-Azo-CN but could not be observed in MWCNT, which further verified that HA-Azo-CN was successfully attached to the MWCNT. The HA-MWCNTs were observed under a transmission electron microscope. As shown in Fig. 2(b), a thick polymer layer could be clearly identified on the outside of the MWCNT wall, which also demonstrated the occurrence of self-assembly between HA-Azo-CN and the MWCNT.

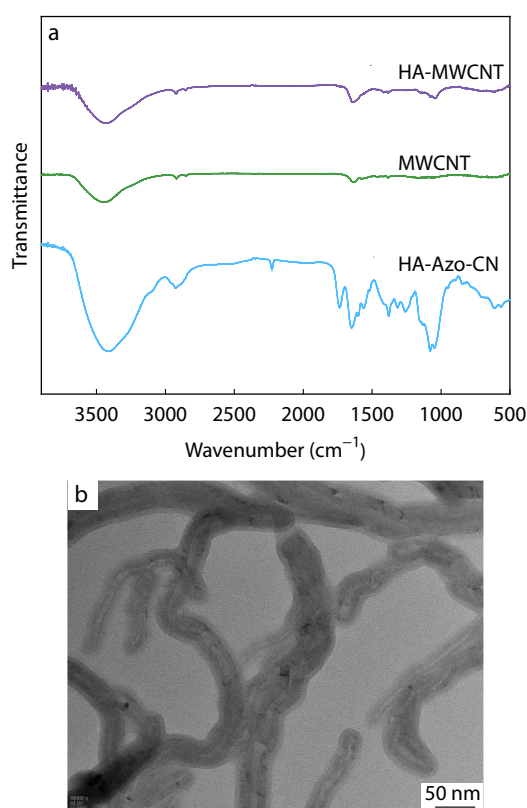


Fig. 2 (a) Infrared spectra of HA-Azo-CN, MWCNT and HA-MWCNT; (b) TEM image of HA-MWCNT.

Dispersion and Photothermal Effect of HA-MWCNT

Following non-covalent modification, the water dispersion of the HA-MWCNTs was examined. HA-MWCNTs were dispersed in Dulbecco's modified Eagle's medium (DMEM) *via* sonication, and the solution was left undisturbed for four days. As shown in Fig. 3(a), no significant precipitation was observed in the mixture, and UV-Vis transmission spectra were obtained to verify the dispersion stability of HA-MWCNTs in DMEM. The transmittance of HA-MWCNTs in DMEM exhibited little change during the four-day period, which further proved the stable dispersion of HA-MWCNTs.

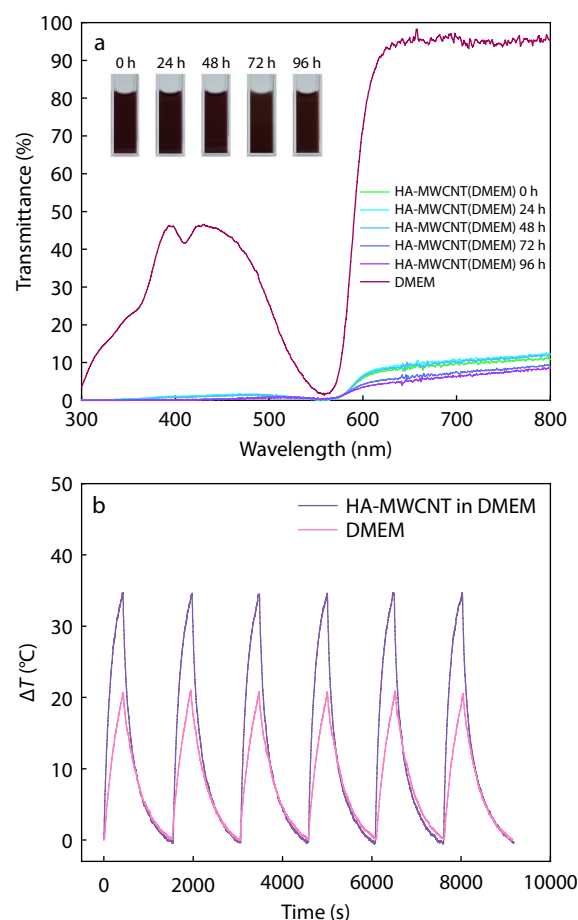


Fig. 3 (a) UV-Vis transmission spectra of HA-MWCNT dispersed in DMEM (100 µg/mL) and pictures of HA-MWCNT dispersed in DMEM (100 µg/mL) for 0, 24, 48, 72 and 96 h; (b) Heating profiles of HA-MWCNT dispersed in DMEM (100 µg/mL) and DMEM subjected to six cycles.

The photothermal effect of HA-MWCNTs plays a crucial role in the photothermal elimination of tumor cells. Therefore, HA-MWCNTs dispersed in DMEM were irradiated with laser light (980 nm, 1.5 W/cm²) for 7 min, and the temperature of the solution was monitored simultaneously. As illustrated in Fig. 3(b), compared to pure DMEM, DMEM containing HA-MWCNT experienced a higher temperature rise, which proved that HA-MWCNT was endowed with excellent photothermal effect and the feasibility of functioning as a photothermal therapy agent.

Photothermal Elimination of HeLa Cells by HA-MWCNT

For a photothermal therapy agent, low cytotoxicity is expected unless it is triggered by laser light. HeLa cells were incubated with HA-MWCNT at different concentrations overnight, and then cell viability was assessed using the MTT assay. As illustrated in Fig. 4, HeLa cells exhibited low cytotoxicity when treated with HA-MWCNTs in the absence of laser light irradiation. After fluorescence staining, as shown in Fig. S4 (in ESI), HeLa cells with green fluorescence were predominant, while HeLa cells with red fluorescence were scarcely observable, which indicated that the majority of HeLa cells remained in a healthy state after co-cul-

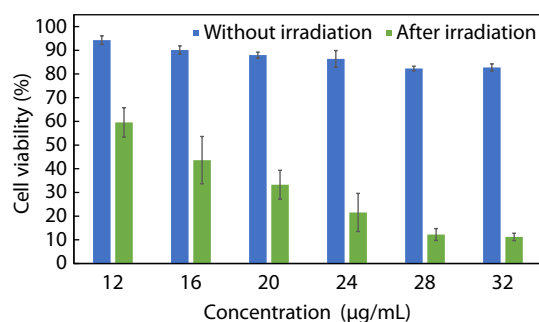


Fig. 4 The cell viability of HeLa cells cultured with HA-MWCNT both without irradiation and after irradiation by laser light.

ture with HA-MWCNTs.

During the co-culture with HA-MWCNTs, mediated by the interaction between hyaluronic acid and CD44 receptors on the surface of HeLa cells, HA-MWCNTs would be absorbed by HeLa cells through endocytosis. Subsequently, after irradiation with infrared laser light, the HA-MWCNTs killed HeLa cells *via* the photothermal effect. To rule out the influence of HA-MWCNTs in the supernatant, as depicted in Fig. 5, the supernatant was replaced with DMEM to ensure that the photothermal effect of HA-MWCNTs in the supernatant would not affect HeLa cells. When irradiated by laser light (980 nm, 1.5 W/cm²) for 7 min, HA-MWCNTs endocytosed by HeLa cells triggered a temperature rise and led to cell death. As illustrated in Fig. 4, as the concentration of HA-MWCNT increased, the cell viability decreased significantly, which not only proved that HA-MWCNT was endocytosed by HeLa cells, but also verified the effectiveness of photothermal elimination of HeLa cells.

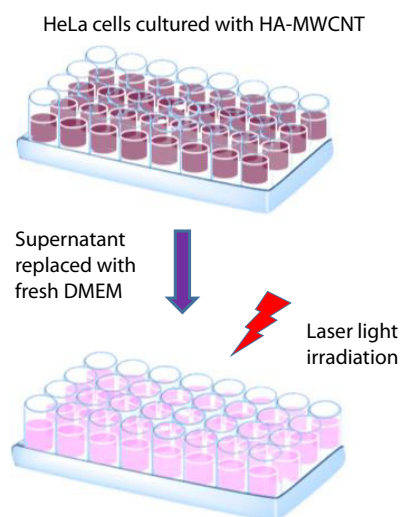


Fig. 5 The procedure of culturing HeLa cells with HA-MWCNT and irradiating them with laser light.

After fluorescence staining with acridine orange (AO) and propidium iodide (PI), as shown in Fig. 6, with the increase in HA-MWCNT, the number of HeLa cells with red fluorescence increased until cells with green fluorescence disappeared, which also indicated that the cell death rate increased with the concentration of HA-MWCNT, proving the efficacy of pho-

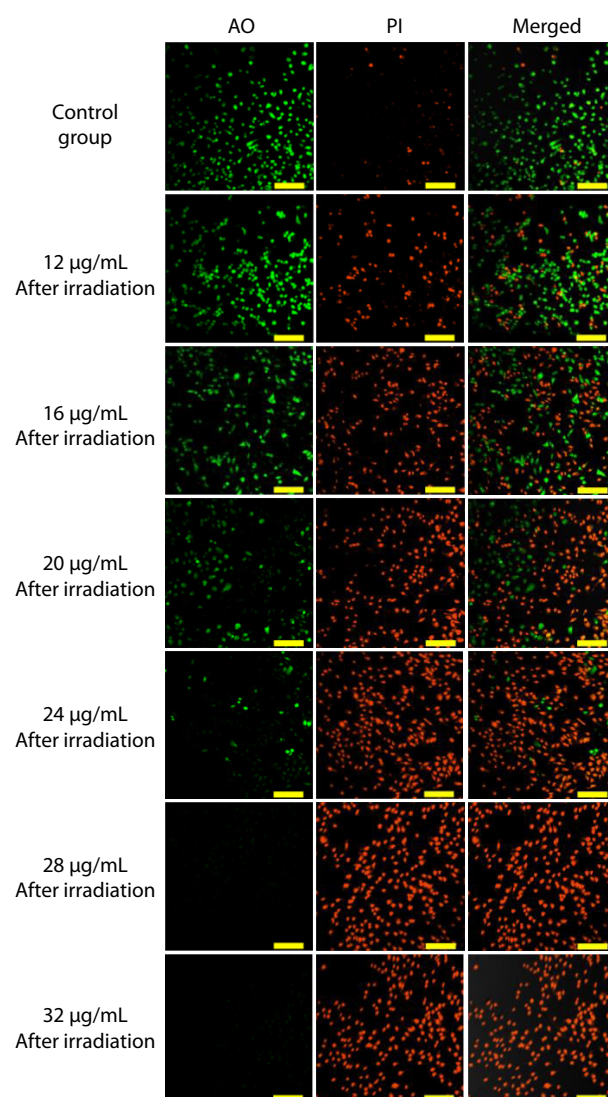


Fig. 6 Confocal images of HeLa cells stained with acridine orange and propidium iodide after co-culture with HA-MWCNT at different concentrations with laser light irradiation (λ_{ex} =488, 562 nm; λ_{em} =500–550 nm, 570–620 nm; scale bar=200 µm).

tothermal elimination using HA-MWCNT.

CONCLUSIONS

In summary, we developed a facile approach to disperse multi-walled carbon nanotube in aqueous systems *via* self-assembly with HA-Azo-CN through π - π interaction and hydrophobic interaction. The modified HA-MWCNTs were endowed with excellent dispersion stability and photothermal effects in an aqueous system. By means of the binding between hyaluronic acid and CD44 receptors overexpressed on the surface of tumor cells, HA-MWCNT was applied in the photothermal elimination of tumor cells. After co-culture with HeLa cells, HA-MWCNTs exhibited minimal cytotoxicity in the absence of irradiation. However, after irradiation with infrared laser light, as illustrated by both MTT assay and fluorescence staining, the death rate of HeLa cells increased with an increase in the concentration of HA-MWCNTs,

which verified the potential of HA-MWCNT as a viable photothermal agent in cancer treatment.

Conflict of Interests

The authors declare no interest conflict.

Electronic Supplementary Information

Electronic supplementary information (ESI) is available free of charge in the online version of this article at <http://doi.org/10.1007/s10118-025-3393-8>.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding authors upon reasonable request.

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