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Research paper

Photoresponsive smart hydrogel microsphere via host-guest interaction for 3D cell culture

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HIGHLIGHTS

- A kind of photoresponsive hydrogel microsphere for three-dimensional (3D) cell culture is prepared.
- This kind of photoresponsive hydrogel is based on the host-guest interaction of β-cyclodextrin and azobenzene.
- This photo-switchable surface can achieve the controllability of cells adhesion and detachment through UV irradiation.

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ABSTRACT

In this study, we designed a kind of photoresponsive hydrogel microsphere for three-dimensional (3D) cell culture, which is based on the host-guest interaction of β-cyclodextrin (β-CD) and Azobenzene. The hydrogel microsphere consists of polyethylene glycol (PEG) and β-CD modified poly(methyl vinyl ether-alt-maleic acid) (PMVE-alt-MA) which was allowed to assemble with azobenzene-arginine-glycine-aspartate (Azo-RGD) via host-guest interaction for controlling cell adhesion and detachment. UV irradiation led to the detachment of Azo-RGD from hydrogel microsphere, and the number of cells cultured on the hydrogel microsphere surface was reduced subsequently. This photo-switchable surface can achieve the controllability of cells adhesion and detachment.

1. Introduction

The cell behaviors are affected precisely by all sorts of physical and mechanical factors in cellular microenvironments [1–4], which commonly refer to the places where cells reside. The extracellular matrix (ECM), as cells growth substrates, is an important part of cellular microenvironment, which provides not only physical supports and signal transduction, but also anchoring sites which can maintain cell migration and prevent anoikis [5–7]. Since the ECM is sophisticated, various materials have been explored and used as mimics of the ECM. Among them, hydrogels are promising biomaterials with inherent ability to facilitate the transport of oxygen, nutrients, and other water-soluble metabolites through diffusion and with capability to be tailored to have desirable physicochemical cues similar to the native ECM [8,9]. These features are of particular importance especially when cells are encapsulated in hydrogels, and that can be used as 3D cell culture scaffolds [10–12]. In order to improve the performance of the hydrogel scaffolds, various strategies have been explored to develop new bio-interfaces that used as mimics of the ECM [13,14]. Peptide-based small molecular hydrogels have been demonstrated to be suitable for culture of different cells by several researchers. For example, peptide hydrogels developed by Zhang et al. [15–17], peptide amphiphilic hydrogels developed by Stupp et al. [18,19], and multidomain peptide hydrogels developed by Hartgerinket et al. [20–22] were all found to be well suited for cell culture and stem cell controllable differentiation. These processes based on the self-assembled monolayers (SAMs) technology could introduce bio-specific adhesion motifs on the hydrogel surfaces [23–25]. Ding et al. [26] designed SAMs and achieved immobilization of RGD peptides on the SAMs which pro-

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moted the specific cell adhesion. SAMs that respond to external stimuli, such as light, heat, and voltage are currently the available class of "smart surfaces" in the formation of cell microarray [27–30]. Yang et al. [31] fabricated high-strength photo-responsive hydrogels, which repeated attachment and detachment of cells was realized by the alternate illumination of visible and UV light. Lutz et al. [32] synthesized thermos-responsive oligo (ethylene glycol) SAMs that achieved effective control over cell adhesion within an appropriate temperature range. However, most existing technologies have been relying on 2D rather than 3D cell culture, which is closer to the cell growth microenvironment.

In this paper, we designed a novel "smart hydrogel microsphere" mainly consisting of PEG cross-linked PMVE-alt-MAH-β-CD which allowed to assemble with Azo-RGD via host-guest interaction for controlling the number of cells cultured on the surface. RGD can promote cell adhesion on microsphere surface. Also, the UV irradiation can lead to the detachment of Azo-RGD from hydrogel microspheres, and the number of cells cultured on the hydrogel microsphere surface would be subsequently reduced. Furthermore, the surface of microsphere is curved rather than plane, which can increase the size, mimic the ECM better and achieve a 3D cell culture.

2. Materials and methods

2.1. Materials

Poly(methyl vinyl ether-alt-maleic acid) (PVME-alt-MA) (M_w = 1,080,000, M_n = 311,000, MDW = 3.47) was purchased from Sigma–Aldrich (Shanghai, China); Arginine-Glycine-Aspartate (RGD), 4-Aminoazobene, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC.HCl), N-hydroxy-succinimide (NHS) were all purchased from Aladdin (Shanghai, China); PEG (M_w = 20,000), β-cyclodextrin (β-CD), dimethyl formamide (DMF), *n*-hexane, pyridine, methanol (CH_3OH), acetone, dichloromethane (DCM) were purchased from Sinopharm Chemical Reagent Co., Ltd., Shanghai, China. Other reagents were all commercially available.

2.2. Methods

2.2.1. Synthesis of azobenzene-COOH and azobenzene-RGD

4-Aminoazobene (1.97 g, 10.00 mmol) and succinic anhydride (1.20 g, 12.00 mmol) were dissolved in 25 mL distilled acetone (0.79 g, 10.00 mmol). Then, anhydrous pyridine was added into the solution, and the mixture was stirred for 6 h at 60 °C. The obtained suspension was filtered, and after been dried at 50 °C for 48 h under vacuum drying, azobenzene-COOH (azo-COOH) was obtained [1].

Azobenzene-COOH (136.60 mg, 0.46 mmol) was dissolved in DCM (100 mL), and EDC■HCl (225.00 mg, 1.17 mmol) and NHS (135.00 mg, 1.17 mmol) were added to the solution, which was then stirred for 24 h at the room temperature. Then, peptide (0.40 mmol) was added to the synthetic, stirred for 24 h. After evaporating the DCM, the final product was obtained [33].

2.2.2. Synthesis of hydrogel microspheres

PMVE-alt-MA (780.00 mg, 5.00 mmol) and β-cyclodextrin (113.50 mg, 0.10 mmol) were dissolved in DMF (10 mL). After that, the mixture was stirred for 9 h at 80 °C under the protection of nitrogen. The excess DMF was removed by rotary evaporation. PEG (0.04 mmol, dissolved in 10 mL DI) was added to the mixture and was stirred for 20 min at 80 °C. An amount of 5 mL was taken out of the mixture solution, dropped into silicone oil and stirred for 24 h at 80 °C under mechanical stirring at 600 rpm. The supernatant of clear silicone oil was removed. A certain amount of *n*-hexane was then added to clean the rest of the silicone oil, and repeated washing three times before drying under vacuum [34]. Finally, the cross-linked microspheres were obtained.

2.2.3. Assembling azobenzene-RGD onto hydrogel microspheres

15.00 mg azo-RGD was dissolved in 1.5 mL CH_3OH. This mixture solution was dropped into 13.5 mL distilled and deionized (DI) water. The hydrogel microspheres were put into this mixture and shaken gently at room temperature for 24 h. After assembly, the microspheres were scrupulously rinsed with DI water and dried with a nitrogen stream. The hydrogel/azo-RGD SAMs were obtained [1].

2.2.4. SKOV3 cell culture on the smart hydrogel microspheres

Cell dispersion with a concentration of 2×10^4 cells/mL was first obtained. A given weight of hydrogel microspheres was sterilized UV irradiation. After washing with PBS (pH = 7.4), 20.00 mg of the microspheres dispersion were added to each well of a 96-well culture plate. Then, 100 μL of SKOV3 cell suspensions were added slowly on the microsphere layer, followed by the subsequent addition of culture medium consisting of RPMI-1640. The 96-well culture plate was maintained in an incubator at 37 °C with a humidified atmosphere of 5% CO_2. The culture medium was replaced every 2 days. The morphology of the cells cultured in the matrices was observed by Olympus LX70-140 microscope. The proliferation of SKOV3 cells in hydrogel was measured using CCK-8 assay [35].

3. Results and discussion

3.1. Schematic illustration of cells adhesion on "smart hydrogel microsphere"

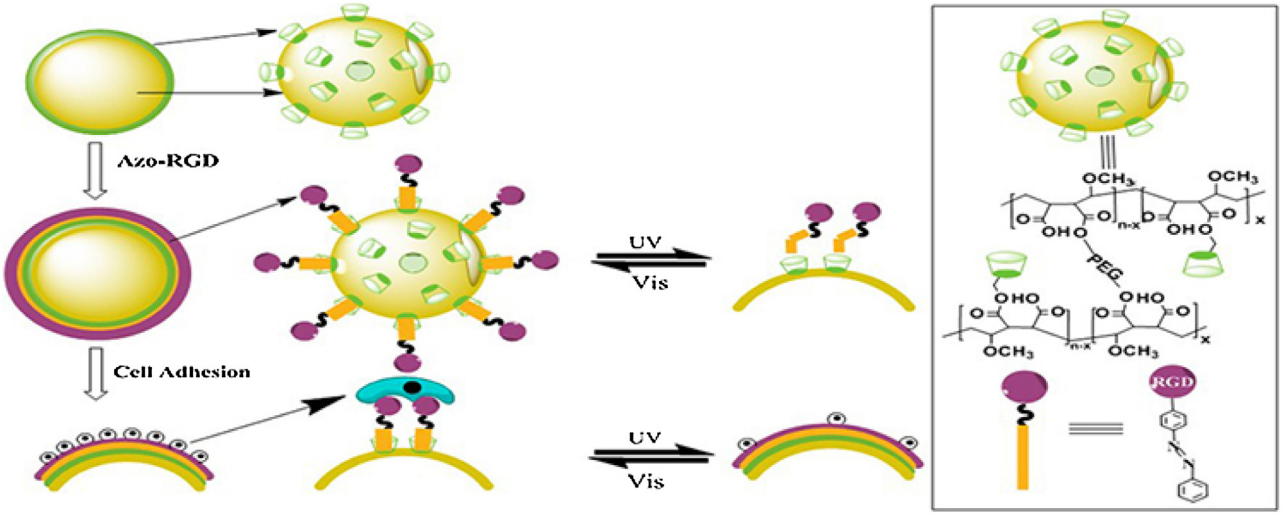
The schematic illustration of the "smart hydrogel microsphere" is shown in Scheme 1. Here, the host-guest interaction of β-CD and Azobenzene was used to control the cells number on the smart hydrogel microsphere. The β-CD (green monolayer) and azobenzene (orange monolayer) could form inclusion complex via host-guest recognition (assembly step), and cells were being cultured on the substrate. We observed that when *trans*-azobenzene was transformed to *cis*-azobenzene upon UV irradiation at 365 nm, azo-RGD (purple monolayer) and cells were detached from the substrate [36–38].

3.2. Chemical structures and morphology characterization of hydrogel microspheres

Chemical structures of the intermediate and final products were verified by ^{1}H NMR, FTIR, and Energy Dispersive Spectrometer (EDS). Fig. 1 is the ^{1}H NMR spectrum of Azo-COOH and Azo-RGD. It can be seen from Fig. 1, that the Azo-COOH has a distinct peak at 12.19 ppm, which is assigned to the —COOH while the Azo-RGD doesn't reflect this peak.

Fig. 2 shows the ATR-FTIR spectra of PMVE-alt-MA, PMVE-alt-MAH-β-CD and PEG cross-linked PMVE-alt-MAH-β-CD. From Fig. 2, the synthetics of PMVE-alt-MAH-β-CD and PEG cross-linked PMVE-alt-MAH-β-CD both have a peak near 1730 cm^{-1}, which is the absorption band of ester carbonyl according to previous report [39], respectively at 1726 cm^{-1} and 1729 cm^{-1}, while PMVE-alt-MA doesn't reflect this absorption band. The absorption band from 3300 cm^{-1} to 2800 cm^{-1} is established to represent the saturated C—H stretching vibration absorption. It can be seen from Fig. 2, that PEG cross-linked PMVE-alt-MAH-β-CD was successfully synthesized.

The EDS atomic percent analysis on the surface of unmodified hydrogel and modified hydrogel is indicated in Fig. 3 and Table 1. In the modified cases, we analyzed the atomic percent before and after UV irradiation respectively. From Fig. 3 and Table 1, the atomic



Scheme 1. Strategy for cell culture on smart hydrogel by using Host-Guest Assembly of β-cyclodextrin and Azo-RGD.

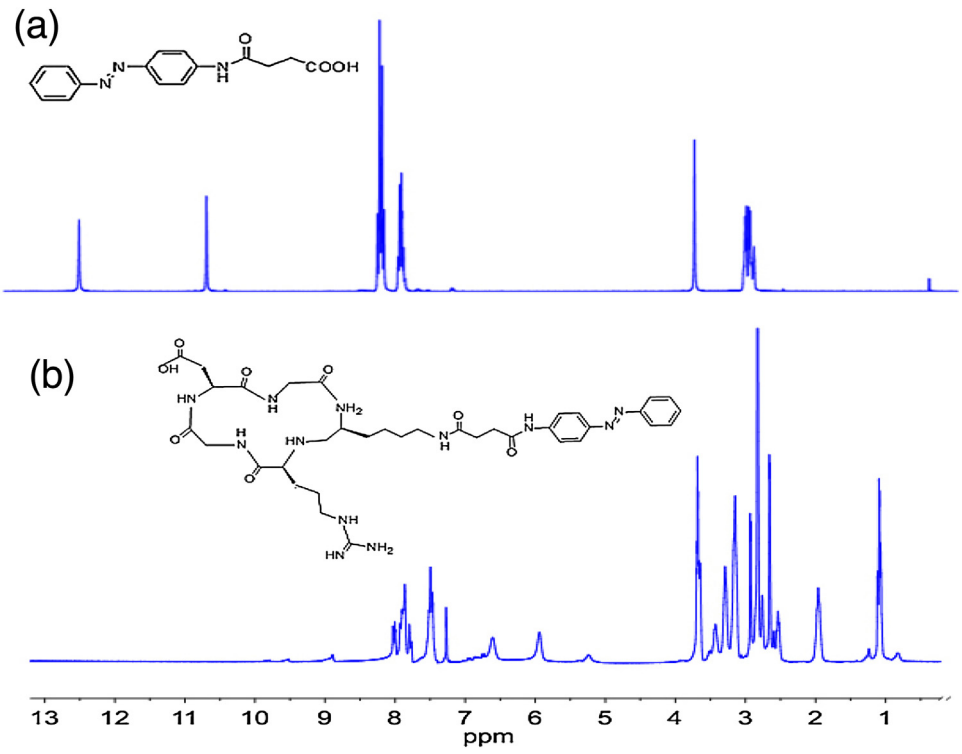


Fig. 1. ^{1}H NMR spectrum of Azo-COOH and Azo-RGD. (a) ^{1}H NMR spectrum of Azo-COOH. (b) ^{1}H NMR spectrum of Azo-RGD.

Table 1
Elemental composition on modified surfaces by EDS analysis.

Chemical element	Control (At%)	RGD modified before UV (At%)	RGD modified after UV (At%)
C	66.47	65.76	62.50
O	33.53	32.62	37.00
N	0.00	1.62	0.50

percent was 1.62% before UV irradiation. After UV irradiation, it became less to 0.50%. This reduction indicates the detachment of RGD from the hydrogel surface since the host-guest interaction of β-CD and Azobenzene. However, there was a little of residual RGD on the surface.

Fig. 4 shows the internal morphology of the hydrogel microspheres. It could be observed from Fig. 4 that the hydrogel was a porous network structure and there were many pores in the hydrogel. This porous microstructure was believed to be beneficial for cell culture as it allows the transportation of both nutrients and waste products in and out of the scaffold. Fig. 5 shows the optical microscope and SEM images of hydrogel microspheres. From Fig. 5, we could see that the hydrogel microspheres have similar size and smooth surfaces.

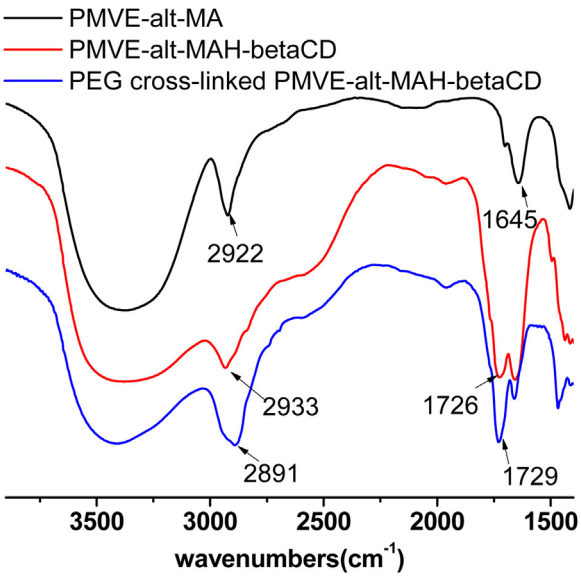


Fig. 2. ATR-FTIR spectrum of PMVE-alt-MA, PMVE-alt-MAH-β-CD and PEG cross-linked PMVE-alt-MAH-β-CD.

3.3. Mechanical property of PMVE-alt-MAH-β-CD-PEG hydrogel film

The mechanical property curves of PEG cross-linked PMVE-alt-MAH-β-CD are shown in Fig. 6. Here, we used PEG cross-linked PMVE-alt-MAH-β-CD hydrogel films' mechanical property to describe the hydrogel's mechanical property. From Fig. 6, the average modulus of elasticity for tension is about 1.43 MPa, and the modulus of elasticity in compression is about 12.78 MPa. From these results, we could distinguish that the hydrogel has an excellent mechanical property.

3.4. Adhesion of SKOV3 cells on hydrogel microspheres

Cells adhesion on hydrogel microspheres is a very crucial factor for cell-hydrogel interaction studies. Therefore, the adhesion behaviors of SKOV3 cells on hydrogel microspheres were investigated in this work too. In order to explore the effects of UV irradiation on the cells adhesion on the smart hydrogel microspheres, 3 kinds of hydrogel microspheres were made. They are the original PEG cross-linked PMVE-alt-MAH-β-CD microspheres, the smart hydrogel microspheres before UV irradiation and smart hydrogel microspheres after UV irradiation (365 nm, 15 w) for 20 min. Fig. 7 are the fluorescence images of cells growth and death situation on different hydrogel microspheres after 7 days of culturing. The C_1 and C_2 are cells growth (green) and death (red) situation on the original PEG cross-linked PMVE-alt-MAH-β-CD microspheres (β-CD SAMs), respectively. The D_1 and D_2 are cells growth and death situation on the smart hydrogel microspheres before UV irradiation (β-CD/Azo-RGD SAMs), respectively. The E_1 and E_2 represent cells growth and death situation on the smart hydrogel microspheres after UV irradiation (β-CD/Azo-RGD after UV SAMs), respectively. Fig. 8 shows the cells proliferation on differ-

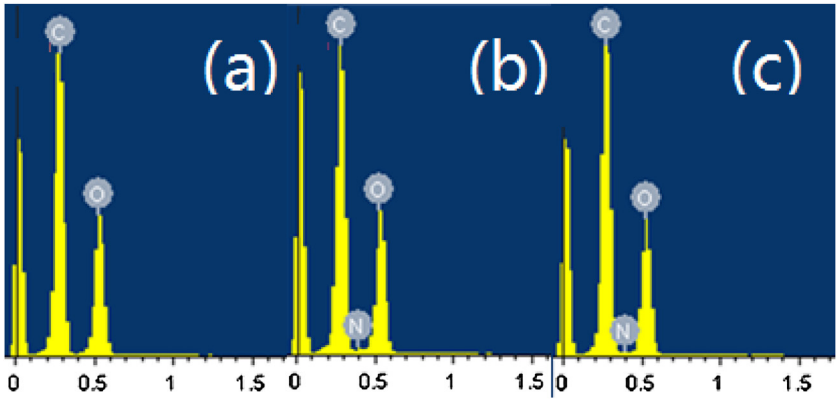


Fig. 3. The EDS analysis of smart hydrogel microspheres. (a) hydrogel of just virgin polymers (PEG cross-linked PMVE-alt-MAH-β-CD); (b) hydrogel of RGD modified before UV; (c) hydrogel of RGD modified after UV.

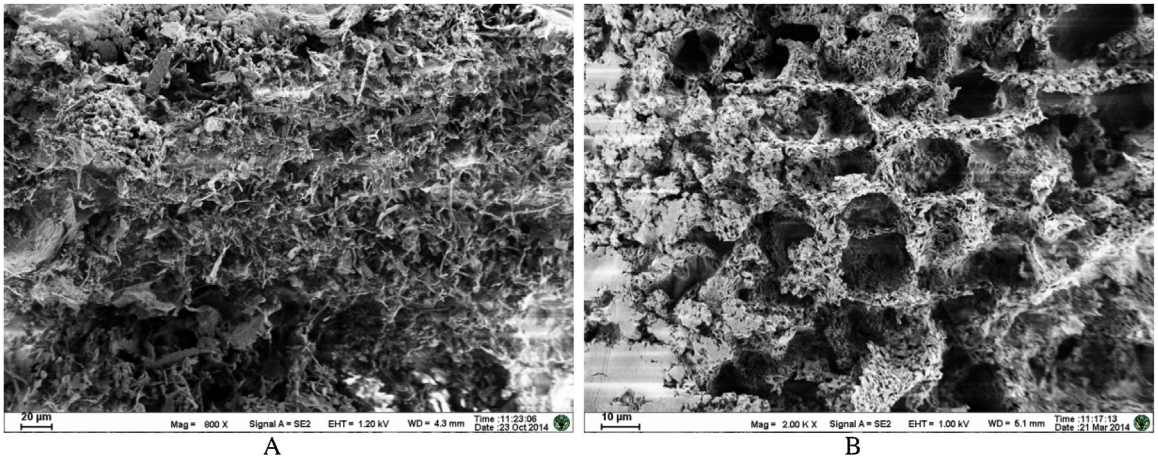


Fig. 4. The SEM images of the hydrogel cross section. (A) captured at ×800 magnification; Scale bar: 20 μm. (B) captured at ×2000 magnification; Scale bar: 10 μm.

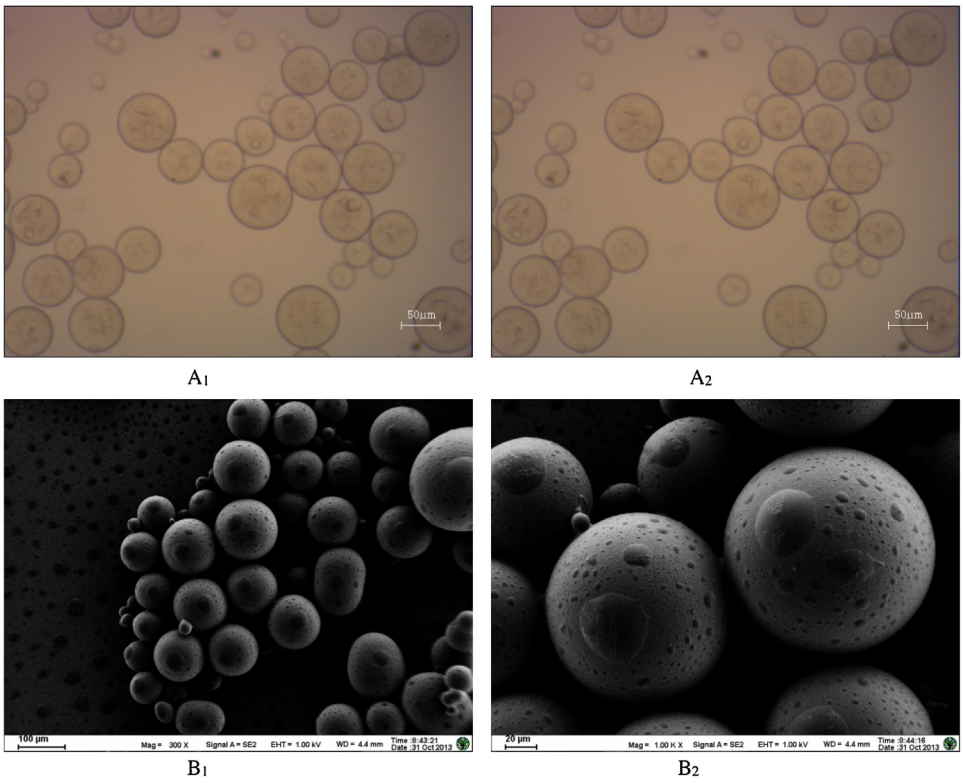


Fig. 5. The optical microscope and SEM images of microsphere hydrogel. (A_1) and (A_2) Optical microscope images; (B_1) and (B_2) SEM images. (A_1) and (A_2) scale bar: 50 μm. (B_1) captured at ×300 magnification; Scale bar: 100 μm. (B_2) captured at ×1000 magnification; Scale bar: 20 μm.

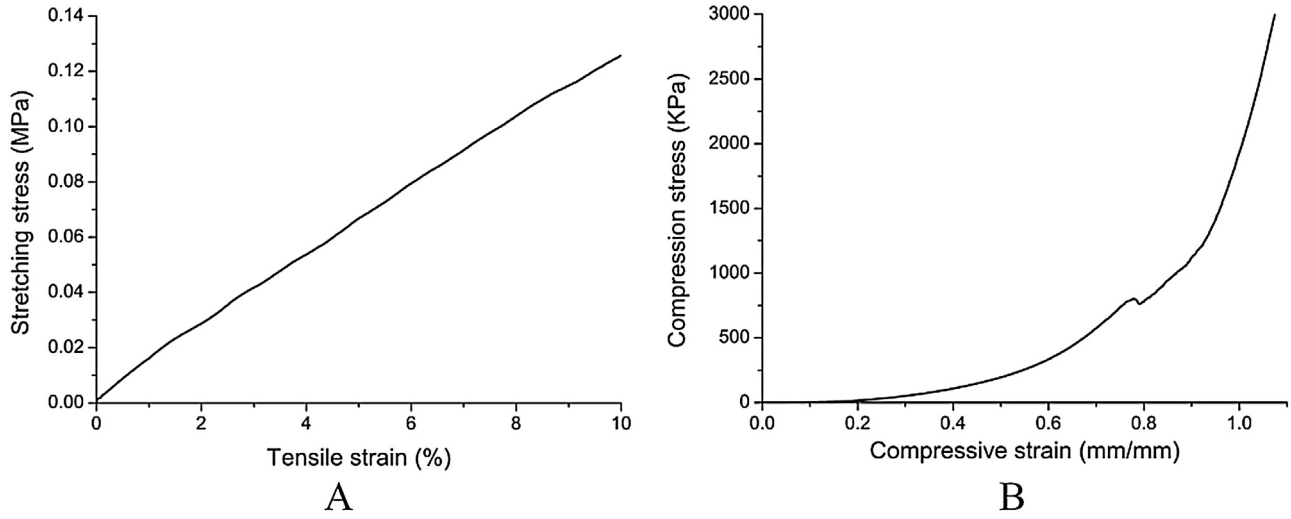


Fig. 6. Mechanical property of PEG cross-linked PMVE-alt-MAH-β-CD. (A) Tensile stress-strain curve; (B) Compression modulus curve.

ent hydrogel microspheres and 96-well culture plates (blank) after 1 day, 4 days and 7 days, respectively. The fluorescence images indicate that the cells adhesion on β-CD/Azo-RGD SAMs microspheres performed best while fewer cells adhered to β-CD/Azo-RGD (UV) SAMs microspheres and the cells number on β-CD was the smallest. These images were consistent with the cells proliferation in Fig. 8. From the cells fluorescence images and cells proliferation on the microspheres surface, we could find that the number of SKOV3 adhered to the surface with the presence of Azo-RGD is much greater than that of after UV irradiation. Therefore, the UV irradiation could control cells number on the smart microspheres.

4. Conclusion

A new hydrogel microsphere which consisted of photosensitive SAMs containing β-CD and azo-RGD have been designed and constructed. Cells could grow well on the constructed microsphere surface. Besides, this surface could also control the cell number

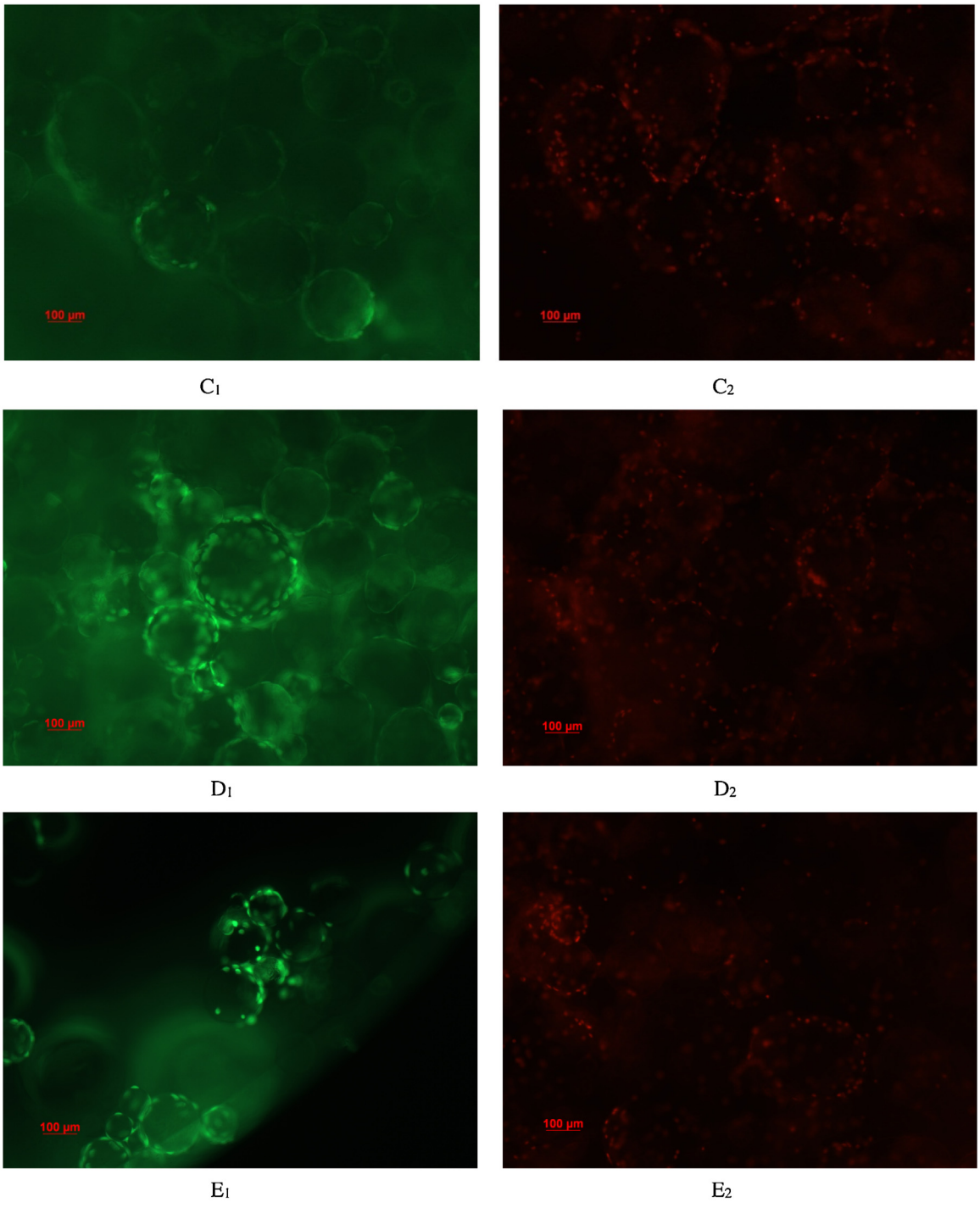


Fig. 7. The fluorescence images of cells growth (green) and death (red) situation on three different hydrogel microspheres after 7 days culturing. (All images were captured at ×100 magnification; Scale bar: 100 μm). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

on the surface upon UV irradiation, based on the host-guest interaction of β-CD and Azobenzene. As the microsphere was in a 3D structure, compared with 2D cell culture, cells growth microenvironment on the 3D surface is closer to ECM. The smart hydrogel microsphere containing β-CD could respond to external trigger and assemble itself with different ligands to obtain different uses. In fact, by immobilizing other bioactive signal such as collagen I on the microsphere, we could mimic some properties of original ECM to study cells further; it could also be used in molecular imaging by incorporating contrast medium. Furthermore, this hydrogel could also be used in drug carriers and tissue engineer. Therefore, this microsphere hydrogel has great potential application in diverse medical and biological fields.

Acknowledgments

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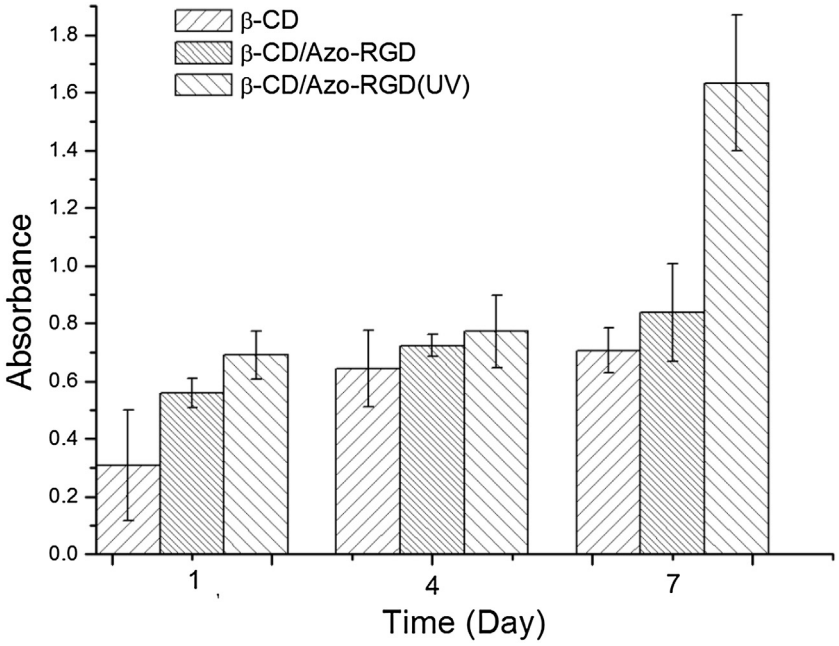

Fig. 8. Proliferation of SKOV3 cells cultured on different microsphere hydrogel as assessed by CCK-8 assays, absorbance at 450 nm.

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