Research Article

Preparation of Gelatin/Polycaprolactone Electrospun Fibers Loaded with Cis-Platinum and Their Potential Application for the Treatment of Prostate Cancer

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Received 9 March 2021; Revised 31 March 2021; Accepted 7 April 2021; Published 22 April 2021

Academic Editor: Songwen Tan

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Although the development of nanomaterials for cancer therapy has received much attention in recent years, prostate cancer still remains one of the most troubling cancers in males. In this work, biomimetic polycaprolactone (PCL)/gelatin (GT)/cis-platinum (CDDP) (PG@CDDP) fibrous films were developed *via* electrospinning technology. The microstructure and chemical properties of PG@CDDP fibers are investigated. It is found that the microscopic morphology and diameter of PG@CDDP fibers are changed compared to those of the PG fibers. The Fourier transform-infrared spectroscopy and wide-angle X-ray diffraction demonstrate that CDDP is successfully incorporated into the fibers. The human prostate cancer cells *in vitro* to electrospun films (PG and PG@CDDP) were evaluated based on initial cell response and cell viability. The density, elongation, and viability of adhered cancer cells significantly reduce with an increased concentration of CDDP in PG fibers. Thus, the developed PG@CDDP fiber matrix has great potential as candidate scaffolds for the treatment of prostate cancer.

1. Introduction

Cancer has been the main cause of human death for centuries due to the uncontrolled proliferation of cancer cells as well as tumor metastasis [1–3]. Particularly, prostate cancer is a common malignant tumor in males and has been regarded as a global issue in developing and underdeveloped countries [4, 5]. Generally, prostate cancer can be described as adenocarcinoma, but it can develop into other histopathological types, e.g., small-cell and neuroendocrine carcinoma [4, 6]. Traditional chemotherapy (e.g., the combination of docetaxel (Taxotere) and prednisone) and radiotherapy are still the

most commonly used strategy in clinical cancer treatment [7, 8]. However, both strategies had some limitations, such as serious side effects, limited therapeutic efficacy, multidrug resistance, and poor efficacy for metastatic tumors [8–11].

Recently, micro-/nanomaterials have gained increasing attention for the treatment of cancer owing to enhanced therapeutic efficiency and relatively mild systemic side effect [8, 11, 12]. In particular, micro-/nanofibers as a bioscaffold have been designed as promising carriers for delivering anti-cancer drugs because of a high loading capacity and high encapsulation efficiency [13–15]. While numerous micro-/nanofabrication strategies, e.g., phase separation, synthetic

FIGURE 1: Schematic diagram of the preparation of PG@CDDP fibers and their interaction with prostate cancer cells.

molding, self-assembly, and drawing, have provided useful tools to prepare ultrafine fiber, in the past decade, electrospinning has received more interest in developing ultrafine polymer fibers for drug delivery applications owing to their extracellular matrix- (ECM-) like structure, excellent biological properties, high mechanical strength, porous mesh with remarkable interconnectivity, high specific surface area, and aspect ratio [16–19]. Electrospun fibrous films can be conveniently implanted into the location of the tumor for the controlled release of chemotherapeutics and ultimately achieve the purpose of curing cancer [20, 21].

Gelatin/polycaprolactone fibers are selected in this study as an anticancer drug delivery system because both polymers possess excellent biocompatible, tunable biodegradable, and nontoxic degradation products [16, 22, 23]. It does not require surgical removal after the completion of drug release. Anticancer drug (cis-platinum) has been widely used as a chemotherapy medication to treat many cancers [24, 25]. In the present work, biodegradable polycaprolactone (PCL)/gelatin (GT)/cis-platinum (CDDP) (PG@CDDP) fibrous films were fabricated *via* electrospinning technology. The morphology and chemical properties of PG@CDDP fibers were investigated by scanning electron microscopy (SEM) and Fourier transform infrared (FTIR) and X-ray diffraction (XRD) spectroscopy. The human prostate cancer cells (T24) *in vitro* that interacted with electrospun fiber films were tested.

2. Experimental Section

2.1. Materials. Cis-platinum (CDDP) was purchased from Macklin (Shanghai, China). Polycaprolactone (PCL) was bought from Aladdin (Shanghai, China). Gelatin (GT) and trifluoroethanol (TFE) were obtained from Sigma-Aldrich (USA). All reagents were of analytical grade and used without further purification. Deionized (DI) water in all experiments was used.

2.2. Preparation of GT/PCL Solutions. Solutions of PCL/GT (PG) were obtained by mixing 10% (*w/v*) PCL/TFE and 10% (*w/v*) GT/TFE at the mass ratio of 1:1 and under stirring for 24 h. To make miscible and transparent PG/TFE solutions, 10 μ L acetic acid was added to the PG solutions according to previous studies [23]. Next, a certain amount of CDDP (i.e., 0.05 g and 0.1 g) was introduced into PG solutions to prepare 10 mL PG@0.5%CDDP and PG@1%CDDP solutions, respectively.

2.3. Electrospinning. Briefly, solutions of PG@CDDP in a 5 mL syringe were delivered at a feeding rate of 1.0 mL/h by a syringe pump (Langer, Baoding, China). A high-voltage power supply (Dongwen, Tianjin, China) of 12.5 kV was used between a blunt metal needle tip and a collector, separated at a distance of 14 cm. All the electrospinning processes were performed on a perpendicular electrospinning strategy at room temperature (21–23°C) with an ambient humidity of 45–50%.

2.4. Scanning Electron Microscopy (SEM). The morphology of PG composite fibers was observed using SEM (VEGA3, TESCAN, Czech). Before imaging, samples were sputter-coated with gold to increase conductivity. The average diameter of PG composite fibers was analyzed by detecting at least 50 fiber segments using ImageJ.

2.5. Fourier Transform Infrared (FTIR) Spectroscopy. A Nicolet iN10 FTIR spectrometer (Thermo Fisher Scientific, Waltham, MA, USA) was applied to detect the FTIR spectra of PG composite fibers over the range of 500–4000 cm^{-1} at a scanning resolution of 2 cm^{-1} during 32 scans.

2.6. X-Ray Diffraction (XRD) Spectroscopy. XRD spectroscopy was carried out to detect the crystal structures of PG composite fibers. The materials were measured between 5 and 80° (2 θ) at a scanning rate of 1.0° (2 θ) per minute.

FIGURE 2: SEM images and fiber diameter distribution of the electrospun fibers of (a) PG, (b) PG@0.5%CDDP, and (c) PG@1%CDDP.

operating with voltage 40 kV and current 30 mA equipped by Cu K α radiation.

2.7. In Vitro Drug Release. 40 mg of PG@0.5%CDDP or PG@1.5%CDDP nanofibers was added in 3 mL of normal saline (0.9%NaCl) and incubated at 37°C in a shaker. At predetermined time intervals, 1 mL aliquots of solution were removed for the measurement and replaced with 1 mL fresh buffer solution. Aliquots of solution were detected using a High-Performance Liquid Chromatography (HPLC) system (Shimadzu, Kyoto, Japan).

2.8. Cell Assays

2.8.1. Cell Culture. Human prostate cancer cells (T24) were purchased from Biyuntian Biological Technology Co., Ltd. (Shanghai, China). Cells were cultured and expanded in

RPMI-1640 supplemented with 10% FBS (Biological Industries, Israel) at 37°C with 5% CO₂ in the air. The cells were harvested at 80–90% confluency from culture flasks by trypsin at 37°C for further subcultures.

2.8.2. Fluorescence Staining. Cancer cells were seeded in 24-well plates at a density of 5.0×10^4 cells/well for 1 d. The cells were fixed with 4% paraformaldehyde for 15 min, rinsed three times with PBS, and then permeabilized with 0.1% X-100 for 6 min. The fixed cells were washed twice with PBS and blocked with 5% bovine serum albumin (BSA) in PBS for 40 min. The cell cytoskeleton and nuclei were labeled with TRITC-phalloidin and 4',6-diamidino-2-phenylindole (DAPI) for 20 min. Cell images were obtained using a fluorescent microscope. The elongation factor of the cell was analyzed as the major axis/minor axis of the cells. By definition, the roundness is equal to 1 for a completely round cell.

FIGURE 3: (a) FTIR spectra and (b) XRD patterns of CDDP, PG, PG@0.5%CDDP, and PG@1%CDDP fibers.

2.8.3. Cell Viability. Cancer cells were seeded in 24-well plates at a density of 3.0×10^3 cells/well for 1, 3, and 5 d. Next, the medium was exchanged with a fresh medium containing 10% Cell Counting Kit-8 (Absin Bioscience Inc., China) and incubated for 2 h. The optical density (OD) values of the medium were measured at 450 nm using a microplate reader.

2.9. Statistical Analysis. All values were shown as mean $\pm$ standard deviation (SD). Statistical analysis was performed using Origin 9. One-way analysis of variance (ANOVA) with Tukey's test was used to identify differences between groups. A value of $p < 0.05$ was considered to be statistically significant.

3. Results and Discussion

3.1. Preparation and Characterization of Composite Fibers. The preparation process of PG@CDDP fibers and their interaction with prostate cancer cells are illustrated in Figure 1. The electrospun GT/PCL couple is one of the most intensively investigated natural-synthetic hybrid fiber systems owing to its excellent electrospinnability, ECM-like structure, favorable biological properties, sufficient mechanical strength, and capability for drug loading.

The morphology of nanofibers plays a critical role in their (bio)physicochemical properties, such as mechanical strength, biodegradation, and cell responses [26–29]. The morphology of composite fibers was observed by SEM (Figure 2). As shown in Figure 2(a), the prepared fibers were highly uniform and smooth with an averaged diameter of 1.528 ± 0.469 nm. When 0.5% CDDP was added into the PG system, there was no significant difference in the fiber diameter between PG@0.5%CDDP fibers and PG fibers (Figure 2(b)). However, the microstructure of PG@0.5%CDDP fibers greatly changed compared to that of the PG fibers. And small particles among the fibers were found in the PG@0.5%CDDP system, probably due to the formation of phase separation after the

FIGURE 4: *In vitro* release of CDDP from PG@0.5%CDDP and PG@1%CDDP fibers.

addition of CDDP. With an increased amount of CDDP, the diameter of PG@1%CDDP fibers slightly reduced as compared to those of the PG and PG@0.5%CDDP fibers. Small particles among the PG@1%CDDP fibers significantly decreased compared to those among the PG@0.5%CDDP system. Taken together, these results indicate that the microstructure of PG fibers was dependent on the introduction of CDDP.

The chemical groups of PG-based composite fibers were analyzed by FT-IR. Figure 2(a) shows the FT-IR spectra of CDDP, PG fibers, PG@0.5%CDDP fibers, and PG@1%CDDP fibers. In the CDDP group, the typical band at $3200\text{--}3283\text{ cm}^{-1}$ belonged to the asymmetric and symmetric tensile vibrations of N–H; the typical band at $1300\text{--}1618\text{ cm}^{-1}$ was assigned to the symmetric and asymmetric bending vibrations of H–N–H; the peak at 800 cm^{-1} corresponded to the tensile vibration signal of N–Pt [30].

FIGURE 5: (a) Fluorescent images of blank, PG, PG@0.5%CDDP, and PG@1%CDDP fibers after 1 d of cell culture. (b) Cell density and (c) cell elongation on blank, PG, PG@0.5%CDDP, and PG@1%CDDP fibers.

In the PG group, the typical bands for peptide bonds from GT were found [31], e.g., amide-A band at $3200\text{--}3500\text{ cm}^{-1}$ corresponding to N–H stretching vibrations, the amide II band corresponding to 1534 cm^{-1} , and the amide III band corresponding to 1239 cm^{-1} ; the typical bands from PCL were found, e.g., the peak at 1700 cm^{-1} corresponding to C=O asymmetric, the peak at 2920 cm^{-1} corresponding to C–H asymmetric, and the peak at 2840 cm^{-1} corresponding to C–H symmetric [32]. The spectra of PG@0.5%CDDP and PG@1%CDDP fibers include all of the characteristic peaks of PG. Particularly, the peak at 800 cm^{-1} in PG@0.5%CDDP and PG@1%CDDP fibers was detected, indicating that CDDP was successfully loaded into PG fibers.

The XRD patterns of CDDP and PG-based fibers are shown in Figure 3(b). The CDDP had obvious crystallization peaks between 10° and 20° [33]. The PG group possessed characteristic diffraction peaks between 20° and 25° [22, 23]. When PG was loaded with different concentrations of CDDP, the PG@0.5%CDDP and PG@1%CDDP fibers showed the characteristic diffraction peak of CDDP at $10\text{--}20^\circ$, and the typical diffraction peak of PG appeared between 20° and 25° , also suggesting that CDDP was successfully loaded into PG fibers.

An initial burst release of PG@0.5%CDDP fibers was detected within the first 1 h (70% of the drug was released), followed by a sustained release profile (Figure 4). Similarly, there was an initial burst found in release in the PG@1%CDDP fibers (77% of the drug was released). A sus-

tained release in PG@1%CDDP fibers was observed with increasing the time from 0 to 12 h.

3.2. Anticancer Behavior of PG-Based Composite Fibers. Cancer cell adhesion is the initial response to the microenvironment, which precedes other cellular behaviors, e.g., spreading, migration, and proliferation [34, 35]. The composite fibers were tested *in vitro* for their anticancer behaviors against human prostate cancer cells. Initial cell response on all samples after 1 d was measured with a fluorescence staining of the actin cytoskeleton and nucleus. It was found that the PG fibrous films containing CDDP greatly affected the attachment and morphology of cancer cells (Figure 5(a)). With an increased amount of CDDP from 0 to 1%, the number of adhered cells gradually decreased and the expression of the actin cytoskeleton (red) reduced.

To better understand the effect of PG@CDDP fibers on the initial behavior of cancer cells, cell density, elongation, and area per cell were quantified by the analysis of the positively stained cells. Figure 5(b) displays that the density of cancer cells significantly decreased with increasing the concentration of CDDP in PG fibers, indicating that the released CDDP from PG fibers greatly inhibited the attachment of cancer cells. Cell elongation is an essential morphological feature for the interaction between cells and biomaterials by mediating the cytoskeleton actin and stimulating the cell nucleus, affecting cell migration, viability, and proliferation [36, 37]. Figure 5(c) shows that the cell elongation of PG-

FIGURE 6: The viability of cancer cells on blank, PG, PG@0.5%CDDP, and PG@1%CDDP fibers after 1, 3, and 5 d of cell culture.

based fibers was significantly reduced compared to that of the blank, which suggests that PG-based fibers could suppress the migration of cancer cells.

The CCK-8 viability assay was performed after 1, 3, and 5 d of incubation. As shown in Figure 6, after 1 d of incubation, the OD value decreased with an increased concentration of CDDP in PG fibers, indicating that the addition of CDDP in PG fibers had a negative effect on the viability of cancer cells. After 3 and 5 d of incubation, the viability of cancer cells displayed a similar trend with that of 1 d of incubation. Taken together, the designed and prepared PG@CDDP fibers significantly inhibited cell attachment and viability, having great potential for the treatment of prostate cancer.

4. Conclusions

In summary, a PG@CDDP fibrous matrix was successfully fabricated using the electrospinning strategy. CDDP was introduced into the PG fibers based on the measurements of FT-IR spectroscopy and XRD. Small particles were found in PG@CDDP fibers compared to the PG fibers due to the addition of CDDP. The diameter of PG@1%CDDP fibers slightly reduced compared to those of the PG and PG@0.5%CDDP fibers. An initial burst release of PG@1%CDDP fibers within the first 1 h was found, followed by a sustained release profile from 0 to 12 h. The density, elongation, and viability of adhered cancer cells significantly decreased with increasing the concentration of CDDP in PG fibers. Therefore, the prepared PG@CDDP fiber matrix shows great potential for the treatment of prostate cancer.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no competing financial interest.

Acknowledgments

The authors are very grateful for the financial support by Key Research and Development Plan of Shandong Province (No. 2018GSF118127), the National Natural Science Foundation of China (Nos. 81602226, 81202016), Shandong Provincial Natural Science Foundation (Nos. ZR2015HQ002, ZR2020QH069), Shandong Province Medical and Health Science Technology Development Project (No. 2019WS464), and China Postdoctoral Science Foundation (Nos. 2016M590638, 2016M590641).

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