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Self-coated interfacial layer at organic/inorganic phase for temporally controlling dual-drug delivery from electrospun fibers

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ABSTRACT

Implantable tissue engineering scaffolds with temporally programmable multi-drug release are recognized as promising tools to improve therapeutic effects. A good example would be one that exhibits initial anti-inflammatory and long-term anti-tumor activities after tumor resection. In this study, a new strategy for self-coated interfacial layer on drug-loaded mesoporous silica nanoparticles (MSNs) based on mussel-mimetic catecholamine polymer (polydopamine, PDA) layer was developed between inorganic and organic matrix for controlling drug release. When the interface PDA coated MSNs were encapsulated in electrospun poly(L-lactide) (PLLA) fibers, the release rates of drugs located inside/outside the interfacial layer could be finely controlled, with short-term release of anti-inflammation ibuprofen (IBU) for 30 days in absence of interfacial interactions and sustained long-term release of doxorubicin (DOX) for 90 days in presence of interfacial interactions to inhibit potential tumor recurrence. The DOX@MSN-PDA/IBU/PLLA hybrid fibrous scaffolds were further found to inhibit proliferation of inflammatory macrophages and cancerous HeLa cells, while supporting the normal stromal fibroblast adhesion and proliferation at different release stages. These results have suggested that the interfacial obstruction layer at the organic/inorganic phase was able to control the release of drugs inside (slow)/outside (rapid) the interfacial layer in a programmable manner. We believe such interface polymer strategy will find applications in where temporally controlled multi-drug delivery is needed.

1. Introduction

Tissue repair and regeneration right after tumor resection are critical in cancer therapy [1]. In order to address the issue of post-surgical local tumor recurrence, the strategy of long-term anti-cancer drug delivery along with short-term anti-inflammatory drug release at the tumor resection site has been proposed [2,3]. In this system, the anti-inflammatory drug may decrease the risk of inflammation and cancer recurrence by inhibiting inflammatory cell growth and the anticancer drug destroys the tumor cells. Moreover, the biodegradable scaffolds provide suitable microenvironment for normal cell growth and so support tissue regeneration. Hence, it is appealing to develop an implantable local drug delivery device with individual release profiles of anti-inflammatory and anti-cancer drugs for cancer patients after tumor resection.

Electrospun micro/nanofibers with effective drug-loading capability and good biocompatibility have attracted much attention for applications in locally controlled drug release and tissue regeneration due to the simplicity of their fabrication scheme, the variety of suitable materials for fiber fabrication, the possession of high surface area and an interconnected pore structure, *etc.* [4–11]. Properly designed electrospun fibers may thus be employed as therapeutic scaffold materials with long-term anti-tumor activity, provided that the fibers have the capability to release anti-inflammatory and anti-cancer drugs sequentially and sustainably. Most studies now focus on embedding an individual drug species in electrospun fibers and controlling its release behavior for postsurgical cancer treatment [12–15]. For example, Zheng et al. mixed anticancer drug doxorubicin (DOX)-loaded inorganic rod-like nano-hydroxyapatite (n-HA) particles in poly(lactic-*co*-glycolic acid) (PLGA) solution to prepare electrospun hybrid nanofibers. The release of DOX from

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this system lasted only for 30 days possibly due to the surface absorption of DOX to HA [16]. Currently, an increasing number of studies have demonstrated that multi-drug loading and the temporally programmable release of each drug has become important criteria in cancer therapy [17,18]. In one study, Yang et al. fabricated electrospun polyvinyl alcohol nanofibers containing hydrophobic curcumin-encapsulated micelles assembled from biodegradable poly(ethylene glycol)-polycaprolactone copolymer and hydrophilic DOX. The release behaviors from this system showed a time-programmed release of hydrophilic DOX (short-term) and hydrophobic curcumin (long-term) [5]. However, the short-term DOX release lasted only for 10 days whereas the long-term curcumin release lasted for as short as 30 days, which was insufficient for long-term tumor healing. It is considered a great challenge to achieve controlled release of multi-drug with distinct properties in a sequential as well as sustained manner and few studies have been reported on this aspect [6,8].

In order to achieve long-term sequential drug release for synergistic cancer therapy, our group previously reported a new core/shell structured drug delivery system of electrospun organic poly(L-lactide) (PLLA) fibers (sheath) containing inorganic MSNs (core) with long term drug release properties due to extended drug diffusion route [19,20]. Nevertheless, initial burst release still existed because of free drugs outside the MSNs and release of multi-drug has not yet been reported.

To achieve the concept of controlled release of two drugs in a common electrospun fiber, herein novel strategy of self-coated interfacial obstruction layer on drug-loaded MSNs based on mussel-mimetic catecholamine polymer (polydopamine, PDA) was designed between the inorganic (MSNs) and the organic (PLLA) phase. The MSNs loading anti-cancer DOX (DOX@MSNs) were first self-assembled using PDA in water solution under mild conditions (DOX@MSN-PDA). The PDA coating on DOX@MSNs was expected to reduce the initial burst release of DOX and further extend its release. Then, we developed implantable PLLA fibers containing naked anti-inflammatory model drug Ibuprofen (IBU) [19,21] and DOX@MSN-PDA by electrospinning (DOX@MSN-PDA/IBU/P) (Fig. 1). Such drug-loading system was conceived to overcome the weakness of the previous system and allow for controlled release of two drugs and extending drug release time from electrospun fibers. Compared to the traditional drug-loaded electrospun fibers, the interfacial obstruction layer in electrospun fibers may allow more ready access to achieve temporally controlled delivery of dual drugs located inside/outside mesopores of MSNs. The physical and chemical properties, drug encapsulation, and *in vitro* drug release from the hybrid fibers were investigated. The potential application of these hybrid fibers for postsurgical cancer therapy was evaluated *in vitro* against inflammatory macrophages, cancerous HeLa cells and normal stromal fibroblasts.

2. Materials and methods

2.1. Materials

PLLA (M_w = 50 kDa, M_w/M_n = 1.6) was synthesized in our laboratory [14,20]. Cetyltrimethylammonium bromide (CTAB, 99%), dichloromethane (DCM), ammonium fluoride, hexafluoroisopropanol (HFIP), ethanol (EtOH) and tetraethyl orthosilicate (TEOS, 98%) were of analytical reagent grade and purchased from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, China). Doxorubicin·HCl (DOX) was purchased from Sangon Biotech (Shanghai) Co., Ltd. (Shanghai, China). Dopamine hydrochloride (98%) was purchased from Aldrich.

2.2. Preparation of mesoporous silica nanoparticles (MSNs)

Mesoporous silica nanoparticles (MSNs) was synthesized according to modified Stöber method [14,20,22]. Briefly, 1.82 g CTAB cationic surfactants for templating purpose was dissolved along with 3.0 g NH_4F catalyst in 500 ml deionized water. The mixture was placed in an 80 °C water bath and vigorously stirred. After the mixture became a clear solution, 9 ml TEOS, which was a source of silica, was added to the solution followed by a 1-h reaction time period. The solution was then centrifuged in order to collect the resultant white porous silica precipitate, which subsequently underwent ethanol washes and drying process in an 80 °C oven for 24 h. Finally, CTAB template was removed using an acidic-extraction method (8 ml 1 mol/L HCl/400 ml ethanol solution) and the resultant MSNs were air-dried until futher use. The particle size distribution of the synthesized MSNs was analyzed using particle size analyzer (Nano ZS, Malvern Instruments Ltd.).

2.3. Development of DOX@MSN and DOX@MSN-PDA

200 mg as-prepared MSNs were added into 20 ml of 60% methanol fully saturated with DOX, labeled as DOX@MSN. The mixture was stirred for 12 h at 37 °C to allow DOX encapsulation into MSNs. The mixture was then centrifuged to collect the particles,

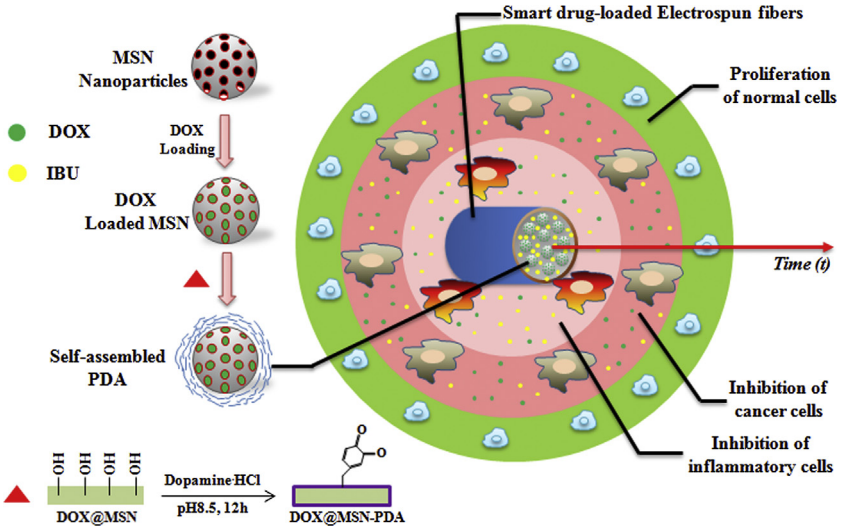

Fig. 1. Schematics of temporally controlling short/long-term dual drug release from electrospun fibrous scaffolds for synergistic cancer therapy.