Theranostics-embedded and Growth Factor-incorporated Multifunctional Scaffolds for Post-surgery Cancer Patients

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Introduction: After surgical removal, new tissues need to be formed at original tumor site to recover body functions for cancer patients and scaffold-based tissue engineering holds great promise for tissue regeneration due to their outstanding advantages [Chen G, *et al., Macromol Biosci*, 2002, 2:67-77.]. To tackle gastrointestinal (GI) tract problem, growth factors like basic fibroblast growth factor (bFGF) could be introduced. However, for many GI cancer patients, another major problem is cancer recurrence after surgery. Multifunctional scaffolds for both tissue regeneration and early detection and treatment for recurrent cancer are therefore required. Gold nanoparticle (AuNP)-based theranostics are new nanodevices that can combine diagnostic and therapeutic functions in one single system for cancers owing to their distinctive properties such as surface enhanced Raman scattering (SERS) effect [Chen R R, *et al., Pharm Res*, 2003, 20:1103-1112.]. In this study, theranostics-embedded and bFGF-incorporated multifunctional scaffolds were fabricated and subsequently assessed.

Methods: Folic acid-chitosan-capped gold (Au@CS-FA) theranostics were made in-house [Guo L., *et al., Proc. 10th WBC*, Montreal, Canada, 2016]. FA can provide specific cancer cell targeting ability. Rhodamin 6G was embedded in the theranostics to generate SERS signals for cancer detection. Theranostics-embedded and bFGF-incorporated multifunctional scaffolds were fabricated using the novel concurrent electrospinning (ES) and co-axial electrospray (C-ES) with a tri-source system, with ES producing nanofibrous PLGA 75/25 scaffolds embedded with C-ES theranostics-encapsulated microspheres and emulsion electrospinning (E-ES) forming bFGF-incorporated PEG-PLGA 50/50 nanofibers. As E-ES nanofibers in multifunctional scaffolds were made of PEG-PLGA 50/50, which degraded faster than PLGA 75/25 nanofibers and PLGA 50/50 microspheres and hence bFGF would release first to promote tissue regeneration. Theranostics would release later for detection and treatment for recurrent cancer. Synthesized theranostics and multifunctional scaffolds were studied using various techniques. SEM images of scaffolds fabricated at different stages were showed in Fig.1. SERS activity of theranostics at different stages were examined. In biological experiments, HeLa cells with high folate receptor (FR) expression and rat gastric smooth muscle cells (rGSMCs) were used to study.

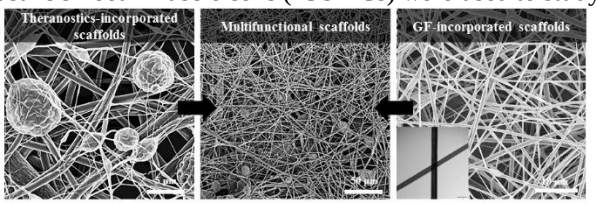

Fig. 1. SEM images of different scaffolds (insert in right image was TEM image of bFGF-incorporated nanofibers).

Results: Synthesized theranostics possessed core-shell structure with many irregular tips on the Au core and a thin layer of CS-FA under TEM observation. The advanced scaffolds incorporated with microspheres were fabricated first and the theranostics-encapsulated microspheres randomly distributed in the scaffolds. After incubation with HeLa cells, controlled release of theranostics occurred when microspheres broke through biodegradation. Fluorescent images of both HeLa cells and MCF-7 cells were displayed in Fig.2a. Strong red fluorescence in HeLa cells could be clearly observed, indicating that released theranostics crossed cell membrane and entered the cytoplasm of HeLa cells through FA-mediated endocytosis. In the control group, only very weak fluorescent signals were shown in MCF-7 cells. TEM analysis for HeLa cells confirmed that released theranostics were taken up by HeLa cells, trapped in endosomes and maintained their original morphology and structure, which indicated the high specific targeting and internalization of theranostics (Fig.2b). SERS spectra of theranostics before encapsulation and after release from both microspheres and advanced scaffolds were displayed in Fig.2c, which indicated strongly simplified Raman signals of released theranostics. SEM image of multifunctional scaffolds after 7 day culture using rGSMCs was shown in Fig.3a. Theranostics were released and cells could be clearly seen in the scaffolds. The proliferation of rGSMCs in multifunctional scaffolds and bFGF-free scaffolds was evaluated using MTT assay. It was observed that sustainedly released bFGF could promote the proliferation of rGSMCs, which indicated promises for improved GI tissue engineering (Fig.3b).

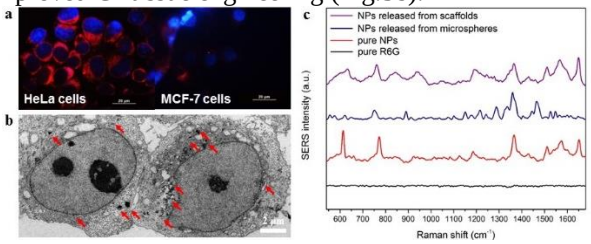

Fig. 2. Properties of released theranostics: (a) Fluorescent images of theranostics in HeLa and MCF-7 cells, (b) TEM image of theranostics in HeLa cells, (c) SERS spectra.

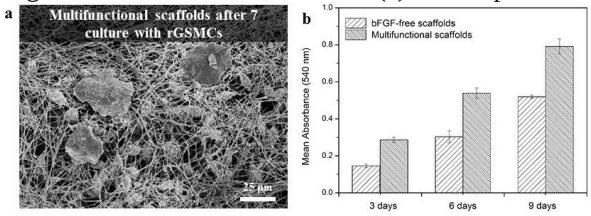

Fig. 3. Structure and property of multifunctional scaffolds: (a) SEM image after cell culture, (b) MTT assay results.

Conclusions: Multifunctional scaffolds with incorporation of Au-based theranostics and bFGF for both tissue regeneration and early detection and treatment for recurrent cancer were successfully developed. Released theranostics could provide high-sensitivity SERS signals and specific cancer targeting ability. Meanwhile, released bFGF could promote the proliferation of rGSMCs.