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Percutaneous fiber-optic biosensor for immediate evaluation of chemotherapy efficacy *in vivo* (Part II): *In vitro* and *in vivo* characterization

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ABSTRACT

A fiber-optic sensor with customized sensing probe made of optical fibers and microcapillaries connected to a low price off-the-shelf portable system was characterized for monitoring the chemotherapy agent induced tumor apoptosis both *in vitro* and *in vivo*. The extrinsic fiber-optic platform is aimed to provide *in vivo* monitoring of non-homogeneously distributed apoptotic biomarker induced by the chemotherapy agent to adjust the tunable delivery of the agent as a personalized chemotherapy system. During apoptosis sensing, fluorescent response of phospholipid conjugated marina blue ($Fluo_{Mb}$, cell distribution indicator) was firstly detected for verifying the cell densities (in the vicinity of sensor probe) were larger than 1×10^7 cells/ml (sensitivity limit), regardless of apoptosis activity (with or without CPA treatment). Fluorescent response of FM 1-43 ($Fluo_{FM\ 1\text{-}43}$, apoptotic activity indicator) was measured later, and applied to indicate the induction of tumor apoptosis by establishing a threshold value as the ratio of two fluorophore emissions ($Fluo_{FM\ 1\text{-}43}/Fluo_{Mb}$, see Part 1), which was 17 from *in vitro* cell culture study and 23.5 from *in vivo* xenografts study. Reproducibility of the sensor detection was found to have a bias lower than 16%.

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1. Introduction

The early assessment of tumor response to chemotherapy at the cellular or molecular level has significant clinical benefits in tailoring personalized medicine for optimal treatment efficacy within a small therapeutic concentration window [1,2]. Most chemotherapy agents are toxins, and it is critical to monitor their efficacy in patients (which differ greatly among individuals and over time) during the procedure for fine-tuning the dosage or agent [1–3]. The response of tumors to chemotherapy is currently monitored by anatomical changes in tumor size several weeks after the initial treatment, which is not efficient for optimal management against evolving, aggressive malignant tumors [1,4–6].

There are currently several molecular imaging/spectroscopy based techniques under development to assess the early response (<72 h of initial treatment) of cancer treatment *in vivo*, including 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) detecting tumor metabolic activity [7,8], dynamic contrast enhanced or diffusion magnetic resonance imaging (DCE MRI or DW MRI) investigating permeability of anti-angiogenesis drugs (transfer rate of contrast agent between tumor interstitial space and plasma), vascular volume or diffusion pattern (apparent diffusion coefficient of water, ADCw) change [9,10], magnetic resonance spectroscopy (MRS) monitoring lipid accumulation [1,11] or the ratio of phosphomonoester/total phosphor [12], and single photon emission computed tomography (SPECT) measuring apoptosis related phosphotidylserine (PS) externalization with an isotope agent (annexin V – ^{99m}Tc) [13,14]. These methods have common disadvantages of requiring expensive facilities and having low availability, which extremely eliminate their capability to provide efficacy monitoring during procedures for fine-tuning the dosage or agent. Lack of clinically required specificity (such as macrophage activity and inflammation interfering with PET detection of metabolic activity [8]) or sensitivity (such as chemotherapy causing deviation quantified by MRI to fluctuate among subjects [10]), risk of radiation exposure (high energy excitation during detection or application of isotopes as contrast agents) add more complexity in transferring these developing methods into actual clinical practice.

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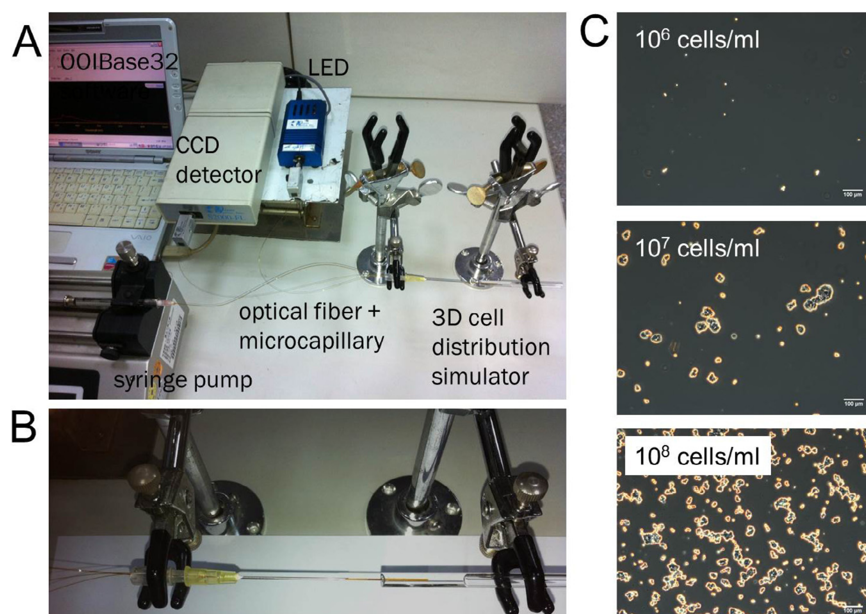

Fig. 1. Fiber-optic apoptosis sensing in a biomimetic simulator with 3-dimensional cell distribution. (A) Appearance of apparatus; (B) Magnified image of biomimetic simulator (MDA-MB 231 cells distributed in polyethylene hydrogel inside a glass chamber) with insertion of fiber-optic sensor probe; (C) Bright field images of cell distributions with different densities loaded on microscope slides with glass covers under the microscope inspection.

We have proposed a fiber-optic apoptosis sensor for evaluating chemotherapy efficacy *in vivo* during the procedure with a 2-fluorophore assay system to monitor PS externalization, which is non-homogeneously distributed on drug induced apoptotic tumor cell membrane surfaces (see Part 1 [15]). Among the 2 exogenous fluorophores, FM 1-43 was chosen as a chemotherapy induced apoptotic activity indicator, and phospholipid conjugated marina blue (Mb, Marina Blue® 1,2-dihexadecanoyl-*sn*-glycero-3-phosphoethanolamine, Mb) was selected as a cell spatial distribution indicator. The fiber-optic sensor detected fluorescent signals indicating apoptotic activities, which were quantified using the ratio of the two fluorescent signals (apoptotic indicator/cell spatial distribution indictor) to eliminate the deviation caused by spatial distribution of cells in the vicinity of the sensor probe (see Fig. 1 and Fig. 2 of Part 1 [15]). The biocompatibility of the silica glass fibers *in vivo* has been proved with very limited foreign body reaction at the implantation sites after 4-week implantation from a pig model study [16]. The anticipated implantation duration of the sensor for chemotherapy evaluation will be no more than 72 h during and after drug administration.

In this study, we characterized performance of the fiber-optic apoptosis sensor both *in vitro* and *in vivo*. In the first portion of the study, the feasibility of FM 1-43 as an apoptotic activity indicator and Mb as a cell spatial distribution indicator were verified with the fiber-optic sensor monitoring the cyclophosphamide (CPA) induced apoptosis of a biomimetic 3-dimensional (3D) cell distribution simulator (MDA-MB 231 cells distributed in polyethylene hydrogel inside a glass chamber as shown in Fig. 1B). The steady-state fluorescence increases of the two fluorophores after interacted with cells were applied to indicate the cell density and CPA treatment dependent correlations. In the second portion of the study, MDA-MB 231 xenografts were applied on the dorsal regions of nu/nu mice 5–6 weeks after inoculation, and then received with the maximal tolerance dosage (MTD) of CPA treatment. The induction of apoptosis in tumor tissue was confirmed by a TUNEL assay. After the two fluorophores were administered into the same xenograft sequentially (Mb then FM 1-43) *in vivo* (Fig. 2A), the ratios of the two steady-state fluorescence increases were compared to find the difference in apoptotic activity of tumor xenografts with or without MTD CPA treatments.

2. Experimental

2.1. Fabrication of sensor probe and assembly of fiber-optic system

The multimode step index optical fibers were purchased from OceanOptics (Dunedun, FL, USA) with 200 ± 4 μm high OH fused silica core, 10 ± 4 μm glass cladding and 200 ± 4 μm thick polyimide buffer coat. The microcapillary were purchased from Polymicro Technologies (Pheonix, AZ, USA) with 50 ± 3 μm inner diameter, 186 ± 6 μm outer diameter, tubing wall composed of fused silica and 16 μm thick polyimide buffer coat. Gauge 20 hypodermic needles and 1c.c. Luer slip tip syringes were purchased from Terumo Corporation (Tokyo, Japan).

The sensor probe (appeared as fiber bundles in Fig. 2B) was composed of two optical fibers and two microcapillaries. One optical fiber was connected to light sources (LS 450 family, OceanOptics, Dunedun, FL, USA) *via* a 250 μm SMA (industry standard SubMiniature version A) adapter with either 35 μW 365 nm lamp for Mb or 45 μW 470 nm lamp for FM 1-43, and the other was connected to an Ocean Optics S2000-FL spectrophotometer with collected spectra analyzed by OOIBase32 software. One end of each microcapillary were adhered to the plastic hub (the hollow bore formed by removing the metal/needle portion in hypodermic needle) UV-curing adhesive (NOV 68, Thorlabs Inc., Newton, NJ, USA), and connected to a syringe pump (Legato 100, KD Scientific Inc., Holliston, MA, USA) by docking the plastic needle hub on the Luer lock tip of a 25 μl gastight syringe (Model. 1702, Hamilton Co., Reno, NV, USA) for delivering either Mb or FM 1-43. The free ends of the 4 fibers were aligned under the inspection of dissecting microscope through the lumen of a gauge 20 hypodermic needle docking on a partially severed plastic syringe barrel (without plunger and the half near the entry of plunger as shown in Fig. 2A), then the portion of the 4 fibers placed in the hollow bore of the syringe Luer slip tip were adhered with UV-curing adhesive.

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